Frontotemporal Dementia

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Colin P. Doherty, Siobhan Hutchinson, Sharon Abrahams, and Robert F. Coen

Abstract Frontotemporal dementia (FTD) is a clinical term that encompasses a spectrum of disorders that affect predominantly language and behavior to varying degrees. Progressive nonfluent aphasia (PNFA) affects mainly language output, semantic dementia (SD) affects mainly language comprehension, and behavioral variant FTD (bv-FTD) affects mainly behavior. FTD is the most common form of young onset dementia. In this chapter, the main clinical, neuropsychological, radiological, and biomarker characteristics are described. Treatment is largely symptomatic but progress in the pathological, molecular, and genetic classification of FTD continues to burgeon, leading to exciting possibilities for disease modification.

Keywords FTD • Semantic dementia • Progressive nonfluent aphasia • Behavioral variant • Social cognition • Tau • TDP-43

Clinical Features of Frontotemporal Dementia

Introduction

In the past 20 years, clinical and basic research have expanded our knowledge of frontotemporal dementia so that it has evolved into a group of overlapping clinical syndromes associated with a range of neurodegenerative pathologies and genetic bases. Clinical–pathological correlation is difficult and by no means definitive. Two patients with a similar clinical syndrome may have different pathologies. Ongoing research into biomarkers will aid disease classification but currently terminology can be confusing as it will often depend upon whether there is a clinical, pathological, or genetic basis to the paper being read. The term frontotemporal dementia is used in two different ways throughout the literature, as is evident even on a cursory comparison of the two major sets of clinical

C.P. Doherty (✉)
Departments of Neurology and Clinical Neurological Sciences, St. James's Hospital and the Royal College of Surgeons in Dublin, Dublin, Ireland
e-mail: cpdoherty@stjames.ie

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diagnostic criteria. Both encompass three prototypic presentations including what has been termed a frontal or behavioral variant, a syndrome of progressive nonfluent aphasia, and a temporal variant characterized by a syndrome of fluent aphasia with associative agnosia referred to as semantic dementia. The site of atrophy is the main determinant of the presenting syndrome. Neary et al. use the umbrella term frontotemporal lobar degeneration (FTLD) for all of the above and reserve the term frontotemporal dementia to refer specifically to the frontal/behavioral variant. In contrast, McKhann et al. use the term frontotemporal dementia (FTD) to refer to all of the above presentations. For the purposes of this chapter, we use the term frontotemporal dementia (FTD) in the general sense of McKhann et al. and the three common subtypes we refer to as behavioral variant FTD (bv-FTD), progressive nonfluent aphasia (PNFA), and semantic dementia (SD). The syndromes that present with language difficulty, PNFA and SD, are often referred together in the literature as primary progressive aphasia but we will discuss them separately here.

History

Arnold Pick is credited with the first description of a progressive disorder of behavior and language associated with circumscribed atrophy of the frontal and temporal lobes. Later, Alois Alzheimer described the classical histological changes associated with "Pick's disease" of interneuronal inclusions and ballooned neurons. In the 1980s, two groups in Lund, Sweden, and Manchester, United Kingdom, published separately large series of patients with frontotemporal atrophy and dementia with prominent behavior and language difficulties. They noted that Pick-type histology was only one of three main histological changes seen and they came up with the first consensus criteria for FTD. At the same time, Mesulam described a series of patients with a progressive language disorder with sparing of other cognitive deficits and non-Alzheimer's pathology, which he termed primary progressive aphasia. Over the subsequent decade, further clinical, imaging, and pathological studies prompted the consensus group to refine the criteria in 1998. They separated the disorders of language, SD and PNFA, from the behavioral disorder (bv-FTD). The separation of the three syndromes has led to concentrated research in each. Genetic advances have been significant and molecules have been identified, which may play a role in pathogenesis (Fig. 6.1). However, significant overlap between the clinical syndromes is still apparent. Indeed, in familial FTD, each of the different clinical syndromes can be seen in the same kindred. Also, in the later stages of each syndrome, patients will often have a mixed clinical picture of behavior, language, and semantic difficulties.

Epidemiology and Demographics

FTD is the third most common form of cortical dementia after Alzheimer's disease (AD) and Lewy body disease. Prevalence studies of FTD have varied results with 15 per 100,000 reported in the UK in the 45–64 years of age group, making it equivalent to AD in this younger age group. However, in the Netherlands, the prevalence was lower at 4 per 10,000

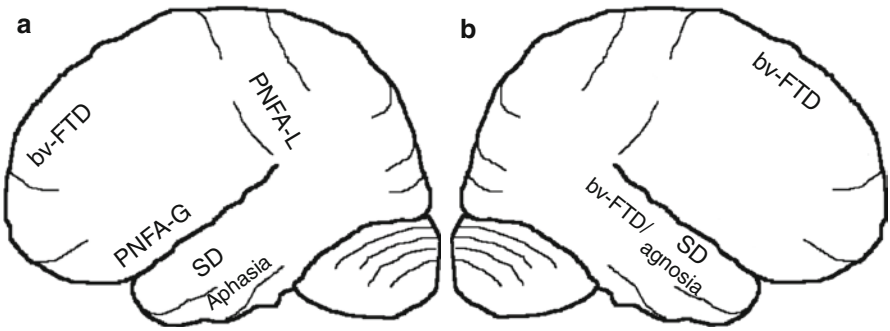

Fig. 6.1 (**a**) Left and (**b**) right view of FTD brain

in the 50–59 years age group. Age of onset is typically younger than other forms of dementia being between 45 and 65 years, though cases are reported outside this range. The incidence in men and women is equal. The duration of illness from onset to death has a range from 2 to 20 years but a mean of 6–8 years. The presence of motor involvement is associated with shortened survival. Familial history of early onset dementia in first-degree relatives is thought to be found in 5–10% of cases. In FTD, bv-FTD is the commonest syndrome affecting 55% of all cases, PNFA accounts for 25% and SD for 20%. Demography does differ between the syndromes: SD has a later age of onset, slower rate of progression, and less frequently reported family history, whereas bv-FTD has the earliest age of onset; most rapid progression and highest reported family history.

Clinical Features

As with other forms of cortical dementia, symptoms are gradual in onset and progressive over time. Patients often do not come to medical attention early on in the disease as frequently behavioral symptoms are excused as midlife change and language symptoms as normal aging (Fig. 6.2).

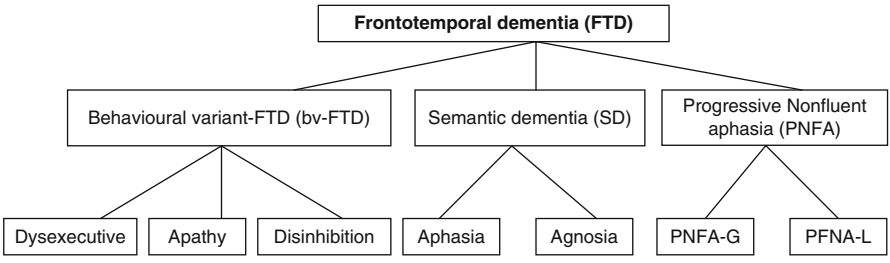

Fig. 6.2 Classification of subtypes of frontotemporal dementia (FTD): Progressive nonfluent aphasia – grammatical (PNFA-G), progressive nonfluent aphasia – logopenic (PNFA-L)

bv-FTD

The clinical features of bv-FTD involve both behavioral and cognitive symptoms. Heterogeneity arises from the fact that bv-FTD can present with at least three distinct syndromes (disinhibited, apathetic, dysexecutive) each linked to discrete frontal–subcortical circuits. Orbitofrontal atrophy is particularly associated with disorders of self-regulation and disinhibition. Dorsolateral prefrontal atrophy gives rise in particular to a dysexecutive syndrome. A more anterior cingulate locus results in pronounced apathy and frontal abulia. Behavioral disorders are common, particularly in frontal and right temporal cases. Both temporal and frontal variants are associated with a loss of empathy, and insight is typically lacking in frontal variant cases.

The presentation is usually due to a change in the patient's behavior noted by their family or friends as lack of insight, or more correctly, lack of concern for their condition. It is usually socially inappropriate interpersonal behavior that is noted initially due to disinhibition of verbal, physical, or sexual impulses and impulsivity. Difficulties with interpersonal conduct are not only due to disinhibition but also due to difficulties with emotional processing and social awareness or social cognition. Patients may lose the ability to express and recognize facial or vocal expressions of emotion, referred to as emotional blunting. In addition, they have difficulty determining what others would think in certain situations; this is referred to as loss of theory of mind. This results in problematic social interactions, an early loss of empathy, and a reduced concern for those around them. These behaviors are seen as out of character by the caregiver and as a significant personality change. It is important to note that for these reasons distress is more common in the caregivers of bv-FTD patients, compared with caregivers of those with other forms of cortical dementia.

In tandem with decline in interpersonal conduct, there is a change in personal conduct that is usually due to inertia or apathy but rarely there may be hyperactivity. Apathy or the loss of drive/initiation is often noted by caregivers and can be mistaken for depression. It is one of the factors that contribute to the decline in personal hygiene and grooming that is frequently reported.

The cognitive symptoms experienced are due to executive dysfunction; therefore, patients have difficulties in planning, problem solving, organization, attention, and mental flexibility. These are symptoms that are not easily identified either by the caregiver or history taker, but a decline in the ability to perform tasks at work and home (activities of daily living or ADL) due to these symptoms is frequently reported. Other symptoms that may be witnessed during the examination or acknowledged by the caregiver when directly questioned include perseverative and stereotyped (ritualistic/compulsive) behavior and speech, altered speech production (aspontaneity), hyperorality and bingeing or overconsumption, and incontinence.

Semantic Dementia

Patients who present with language difficulty will be more aware of this symptom than those with behavioral problems and will frequently complain that they have forgotten the word for things. Memory, however, is not impaired and patients will be oriented, able to keep appointments, learn and remember visuospatial information. The speech of a patient with SD remains fluent, with normal use of grammar; however, there will be hesitation in word finding, loss of vocabulary, and semantic paraphasias and words may be substituted for a vague, nonspecific

term. Speech, therefore, becomes empty with loss of content though not tangential as we see in AD. There is anomia, with loss of comprehension of that word and object, which is demonstrated by being unable to match the object with semantically similar objects or being able to pick an object from description of its use. Knowledge loss appears to affect exemplars first, so a patient may be initially unable to recognize a rabbit, but tell you that it is an animal. Knowledge of more personally relevant objects is more resistant. Repetition is not impaired and patients can repeat multi-syllable words without difficulty. Writing to dictation is unimpaired. Patients with SD develop surface dyslexia in reading where the word is read phonologically correctly but loss of knowledge of the word produces the error (e.g., choir is pronounced "cho–er"). A rarer nondominant form of SD with predominant agnosia (a failure to recognize objects or people) instead of aphasia is increasingly recognized. Patients with nondominant agnosia also appear to have a more behavioral presentation and are more likely to have difficulties with social cognition, becoming withdrawn and losing empathy rather than showing the impulsive disinhibition of bv-FTD (Fig. 6.1b).

Progressive Nonfluent Aphasia

In PNFA, there is a breakdown in spontaneous speech that is noted by the caregiver and examiner. The speech of a patient with PNFA is generally nonfluent with variable loss of grammar and phonemic paraphasias (word substitutions). There will be anomia on direct object naming but knowledge of the object will be intact, distinguishing it from SD. They may be able to pick the correct name from choice and will be able to match the object with others semantically linked to it. Recently, a panel of 20 experts has published consensus criteria for the Classification of Primary Progressive Aphasia and its Variants. In this classification Semantic Dementia remains intact but PNFA has been subdivided. PNFA-G is a predominantly agrammatic form with primary difficulties with grammar, syntax, oral praxis, and fluency. PNFA-L, logopenic progressive aphasia is characterized by fluctuating interruptions of fluency due to word finding difficulties, but with intact syntax and without agrammatism. PNFA-L is rarer than PNFA-G and is associated with episodic memory difficulties (Fig. 6.1a). Interestingly, many described patients have Alzheimer's disease pathology at postmortem. Classification of progressive aphasia can then be further specified as "imaging-supported" if the expected pattern of atrophy is found and "with definite pathology" if pathologic or genetic data are available.

Clinical Examination and Investigations

Clinical examination should focus on qualifying the cognitive deficits specific to each syndrome in addition to noting which cognitive functions are spared. Orientation, calculation, visuospatial skills, and memory should be relatively well preserved early in FTD. This profile of cognitive deficits and preserved function can be reliably demonstrated with clinic-based mental state testing. A variety of rapid clinic-based screening tests are used by clinicians such as:

- *The Montreal Cognitive Assessment* (MOCA) is sensitive to the presence of cognitive impairment and has the advantage of being rapid test that reliably distinguishes pseudodementia. Also, bv-FTD patients may not participate in lengthy testing because of features of their behavioral disorder: apathy, inattention, perseveration, and poor organization.

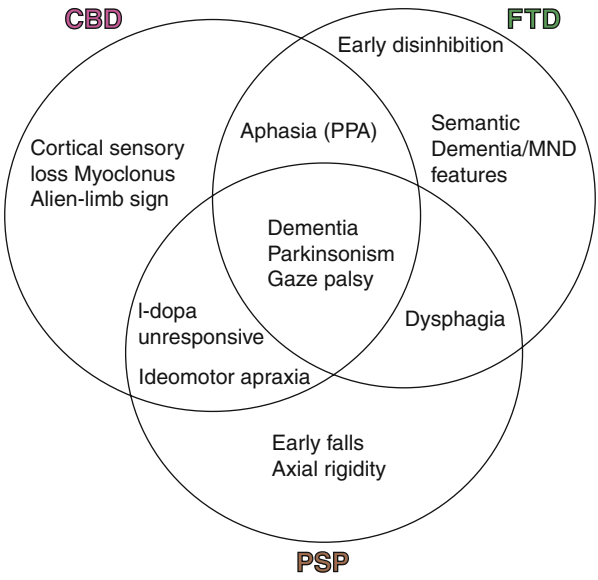

Fig. 6.3 Clinical crossover of frontotemporal dementia, corticobasal degeneration, and progressive supranuclear palsy (Courtesy of Dr. B. Murray, Hermitage Hospital, Dublin)

- *The Addenbrooke Cognitive Examination–Revised (ACE-R)*. This Screening measure takes about 20 min and is sensitive to differences in early AD and FTD.
- *Rey Osterrieth Complex Figure.* Many language-based tests will be impossible in PPA patients and will need to be adapted, for example, memory testing using the Rey Osterrieth figure is more suitable than word list learning.
- *Frontal Assessment Battery (FAB).* May assist in differentiating FTD from non-FTD dementias.
- *Frontotemporal Behavioral Scale (Lebert et al. Based on caregiver interview).* It is useful in bv-FTD to quantify behavioral change by using a measure such as the Frontotemporal Behavioral Scale.

The rest of the clinical examination should focus on the presence of motor signs. FTD is known to overlap with corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) and with amyotrophic form of motor neuron disease (FTD-MND), and 10% of FTD cases may develop MND. The presence of extrapyramidal signs, muscle wasting, fasciculations, or unilateral apraxia adds to the behavioral and cognitive profile in characterizing the syndrome (Fig. 6.3).

Further Tests

- *Biochemical and metabolic laboratory tests.* Blood tests and serological markers that can point to potentially reversible syndromes that may mimic FTD are listed in Table 6.1.
- *Neuropsychological assessment* consisting of a more extensive investigation of the cognitive impairment is important to both qualify and quantify the cognitive profile to aid diagnosis.
- *Electroencephalography* was thought to be normal early in FTD and that this was useful to differentiate from AD, but this has not proved to be a reliable discriminator.

Table 6.1 Laboratory tests for differential diagnosis of FTD

Hematological malignancies with CNS involvement FBC and differential Serum protein electrophoresis Bone marrow aspiration
Biochemical disorders: Wilson's disease; porphyria Electrolytes Renal function tests Liver function tests Urinary and fecal porphyrins
Metabolic or endocrine: Hypothyroidism, adrenoleukodystrophy Thyroid function tests Very long chain fatty acids
Vascular: CADASIL, *MELAS*, *Multiple strokes* Notch 3 mutation MELAS mutation Thrombophilia screen
Infective: HIV dementia, *syphilis*, *PML* HIV testing VDRL/TPHA JC virus
Immunological: Multiple sclerosis, *CNS vasculitis*, *paraneoplastic* Oligoclonal bands Connective tissue work-up TPO antibodies Potassium channel Abs NMDA receptor Abs Anti-GAD Abs
Other degenerative disease: *Creutzfeldt-Jacob disease*, *atypical AD*, *ALS/FTD* EEG and 14–3–3 and s100 proteins in CSF MRI and PET/SPECT EMG

- *Brain imaging* is useful to examine for focal atrophy though requires high-resolution T1 images and even then atrophy may not be notable at presentation. Functional imaging (PET or SPECT) can be useful to distinguish more AD-like from more FTD-like patterns of hypometabolism or hypoperfusion.

Diagnostic Criteria

The diagnostic criteria in FTD have been subject to a number of changes over the years and new consensus criteria are set to emerge soon. The first set of criteria was devised at a consensus meeting in 1996 where it was decided to separate the three clinical syndromes in

Table 6.2 Clinical criteria for frontotemporal dementia

1. The development of behavioral or cognitive deficits manifested by either:
   a. Early progressive change in personality, characterized by difficulty in modulating behavior, often resulting in inappropriate responses or activities.
   b. Early and progressive change in language, characterized by problems with expression of language or severe naming difficulty and problems with word meaning.
2. The deficits outlined in 1a or 1b cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
3. The course is characterized by gradual onset and continuing decline in function.
4. The deficits outlined in 1a or 1b are not due to other nervous system conditions (e.g., cerebrovascular disease), systemic conditions (e.g., hypothyroidism), or substance-induced conditions.
5. The deficits do not occur exclusively during delirium.
6. The disturbance is not better accounted for by a psychiatric diagnosis (e.g., depression).

FTD, and criteria were devised for each. Core diagnostic features that were thought to be integral to each syndrome must be present to make the diagnosis. Supportive diagnostic features were not considered necessary for a diagnosis but were included as being characteristic of the syndrome and "adding more weight" to the diagnosis. Exclusion criteria were listed to prevent the inclusions of other forms of cortical dementia, specifically AD, acute neurological, and psychiatric disorders. All must be absent in order to make a diagnosis.

In the 12 years subsequent to the Neary et al. consensus meeting, clinical study of FTD has questioned the criteria and there are currently calls for revision. Some researchers (Table 6.2) have suggested simplifying the clinical criteria into either behavior or language presentation of FTD and then qualifying this classification further with a neuropathological diagnosis when and if a patient comes to autopsy. However, most researchers in the language presentation of FTD would view SD and PNFA as separate entities. The risk of combining these syndromes is that important clinical findings, including potential biomarkers, are missed because the population studied is heterogeneous. In the debate on "lumping or splitting" diagnoses, the current rationale is to clinically qualify each case as carefully as possible, while attempting to avoid a situation where clinical diagnosis becomes too complicated for clinical practice.

Syndromes That Overlap and Mimic FTD

The FTD syndromes, though defined on cognitive and behavioral criteria, will frequently include motor symptoms and signs. Research has shown the significant pathological and molecular overlap between FTD and other neurodegenerative disorders and hence the crossover in clinical features. Table 6.3 summarizes the syndromes that overlap.

On the other hand, there are a range of clinical disorders that have no pathological overlap but whose clinical phenotype can mimic those of FTD. Table 6.3 summarizes the syndrome that mimics FTD.

Table 6.3 Overlap and mimic syndromes

Overlap syndromes

Corticobasal degeneration (see Chap. 10): CBD is a progressive disorder characterized by asymmetrical motor and sensory cortical and extrapyramidal dysfunction. It is classically associated with tau pathology. Typically, the patient presents to a movement disorder clinic with a "useless arm" due to unilateral rigidity, bradykinesia, apraxia, tremor, and dystonia. Cognitive symptoms have been underreported in CBD but a nonfluent aphasia is now regarded as one of the core features.

Progressive supranuclear palsy (see Chap. 10): PSP or Richardson's syndrome is a quickly progressive disorder of bulbar palsy, supranuclear gaze palsy and axial rigidity, and postural instability causing unexplained falls. However, PSP pathology is associated with a range of clinical syndromes, including a parkinsonian syndrome, CBD, and PNFA. Patients with PNFA, who are found to have PSP pathology, are more likely to have a prominent early apraxia of speech, though notably do not develop other features of PSP. Again, PSP pathology is also seen in bv-FTD but less commonly in SD.

FTD-MND (see Chap. 7): The association between MND and dementia has been described for over a century. After investigation of a series of MND patients with dementia in 1980s, the dementia was characterized as a frontal atrophy with progressive behavioral and dysexecutive change and therefore, the term FTD with MND (FTD-MND) was adopted. Up to 50% of MND may have cognitive or behavioral abnormalities when tested.

Mimic syndromes

Psychiatric illness: Initial presentation with behavioral change is frequently interpreted by the family and medical professionals as a psychological reaction or psychiatric disorder. For example, apathy may be interpreted as depression and irritability or disinhibition as a midlife personality change or secondary to substance abuse. Association with other symptoms of FTD and the time course of "insidious onset and gradual progression" can help differentiate FTD from psychiatric disorders.

Alzheimer's disease (see Chap. 3): AD is also a dementia of insidious onset and gradual progression that has language and behavioral dysfunction. Although the presence of early amnesia should point to a diagnosis of AD and, conversely, early behavioral change is more typical of FTD, later dementia in FTD and AD can be very similar. Some FTD group studies have noted as high as 11% of patients have amnesia at presentation. Similarly, visuospatial skills tend to be preserved in early FTD and impaired in AD.

Vascular dementia (see Chap. 10): Apathy or abulia, frontal executive dysfunction, frontal release signs, and parkinsonian features are common in VD and FTD. Again, the association with other symptoms may help in differentiating the two disorders. However, the stepwise time course and presence of corticospinal tract signs would suggest VD over FTD. MRI may be helpful, indicating FTD if atrophy is focal, lobar atrophy and VD if periventricular ischemia is severe.

Other neurodegenerative disorders: Disorders with cognitive and motor involvement should have distinguishable features (in brackets); differing collections of symptoms and differing time course: Parkinson's disease (tremor); Multisystem atrophy (cerebellar ataxia); Huntington's disease (chorea).

Phenocopies: There are recent reports of patients who have a typical clinical presentation of bv-FTD but who have extremely slow progression. Such cases are described as "phenocopies" and as yet, there is no pathological correlation with such cases. It has been found that abnormal executive function, MRI atrophy, and impaired ADLs are the best discriminators of true bv-FTD from such phenocopies.

Neuropsychology

Given the wide variability of presentations in FTD and the fact that there are a number of other overlapping conditions, neuropsychological assessment can greatly contribute to differential diagnosis. Neary et al. include guidelines regarding the typical neuropsychological findings that characterize the prototypic presentations. Depending on the presenting signs and symptoms, different tailored batteries will be appropriate, but in all cases, there are several core aspects of the assessment that should be emphasized. Given that FTD can frequently present with alterations in behavior and personality, there should not be an over-reliance on cognitive testing per se. Depending on the locus of pathology, patients may do extremely poorly on conventional "frontal lobe" tests such as the Wisconsin Card Sorting Test, Trail Making, and verbal fluency, or they may, in fact, perform normally, yet still show major impairment in self- and social regulation. Therefore, it is essential to obtain good collateral information on everyday behavioral alterations using suitably designed instruments. One such is the Frontal Systems Behavior Scale (FrSBe), which built on Cummings' neuroanatomical model to provide self- and informant-based ratings of apathy, disinhibition, and executive dysfunction both premorbidly and currently. In addition to permitting age and gender graded interpretation of behavior change, the self- and informant-based ratings can be compared to evaluate the degree of insight or lack thereof.

Observation of the patient during interview and testing is also an essential aspect of the assessment. Qualitative analysis is as important as the patient's quantitative performance on neuropsychological tests. For example, patients with Alzheimer's disease (AD) or FTD may perform equally poorly on a visuoconstruction task such as copy of the Rey Osterreith Figure or Block Design, even though constructional praxis and visuospatial integration is typically well preserved in FTD. The quality of performance on task may be more telling, with AD patients typically aware of their difficulties, applying effort, and attempting to rectify errors. In contrast, FTD patients frequently lack awareness or concern regarding poor performance, with cursory effort and little attempt to rectify errors. Task failure in FTD may reflect poor planning and organization, regulation and monitoring of behavior, and attention to qualitative aspects of the patient's performance can aid differential diagnosis.

Some screening tests have been designed specifically for the purpose of discriminating FTD from non-FDT dementias such as the Addenbrooke's Cognitive Examination (ACE-R). It was designed to differentiate AD from FTD using a ratio based on the tendency for AD patients to be more impaired on tests of memory and orientation and less impaired on tests of language and verbal fluency, whereas FTD patients tend to exhibit the opposite pattern. Brief measures designed to assess frontal lobe/executive deficits include the Executive Interview (EXIT) and the Frontal Assessment Battery (FAB), which may assist in differentiating FTD from non-FTD dementias. In contrast, formal neuropsychological assessment entails a much more detailed evaluation of the specific profile of behavioral, cognitive, and emotional alteration, which can assist in identifying FTD variants, discriminating organic from nonorganic causes of behavior change, and in identifying FTD-like features that can be early manifestations of overlap conditions such as MND, CBD, or PSP. A typical selection of neuropsychological tests useful in evaluating FTD and its variants is

Table 6.4 Selected neuropsychological tests useful in assessment of FTD

Wechsler Adult Intelligence Scale (WAIS-IV)
Similarities (verbal abstract reasoning)
Vocabulary (word knowledge)
Matrix reasoning (nonverbal abstract reasoning)
Block Design (visuoconstructional problem solving)
Wechsler Memory Scale (WMS-IV)
Logical memory (story recall)
Visual Reproduction (visual recall)
Rey Osterrieth Complex Figure (copy, delayed recall)
Addenbrooke's Cognitive Examination (ACE-R)
Frontal Assessment Battery (FAB)
Modified Wisconsin Card Sorting Test
Trail Making Test (Part A and B)
Stroop Test
Test of Premorbid Functioning (premorbid intellect vs. surface dyslexia)
Verbal Fluency (semantic categories and FAS test)
Boston Naming Test
Word-picture matching (single-word comprehension)
Pyramids and Palm Trees Test (verbal/visual semantics)
Test for Reception of Grammar (TROG)
Token Test
Boston Diagnostic Aphasia Examination (expression/comprehension subtests)
Iowa Gambling Task
Faux Pas Test
Frontal Systems Behavior Scale (FrSBe)
Frontotemporal Behavioral Scale
Delis-Kaplan Executive Function System (D-KEFS)

provided in Table 6.4. Depending on the depth of detail required, there are also purpose-designed comprehensive batteries to evaluate a broad range of cognitive processes dependent on the integrity of the frontal lobes, most notably the Delis-Kaplan Executive Function System (D-KEFS). However, as is always the case in neuropsychological assessment, the nature and extent of the evaluation will be determined by the referral question and the characteristics of the client.

Patients with an orbitofrontal–ventromedial prefrontal locus of pathology, which may be focal at the onset of bv-FTD, may perform normally on a variety of the tests traditionally considered sensitive to frontal lobe/executive dysfunction but have a profound deficit in everyday decision making and social regulation and behavior change. A number of more experimental cognitive tests have been developed, which are more sensitive to such abnormality The Iowa Gambling Task assesses decision making and learning in high- and low-risk situations. During the task, healthy individuals learn to avoid the risky choices while those with FTD continue to make high-risk choices, which results in an overall net loss. Another recent test sensitive to orbitofrontal dysfunction is the Faux Pas test, based on "theory of mind" (or ability to infer another's thoughts and feelings). Changes in this ability may underlie some of the changes in personality and social functioning frequently

seen in FTD patients. The task entails hearing 20 short stories, 10 of which contain a social faux pas, and 10 of which are neutral. Following each, questions are asked to evaluate the patient's social awareness and social understanding. Patients with bv-FTD, but not patients with AD, do poorly on this test.

Biomarkers

Introduction

Biomarkers are characteristic biological properties that can be detected and measured in parts of the body like the blood or tissue and may extend to brain imaging or neurophysiological tests. They may indicate either normal or diseased processes in the body. Disease-related biomarkers give an indication of whether there is a threat of disease (risk indicator or predictive biomarkers), if a disease already exists (diagnostic biomarker), or how such a disease may develop in an individual case (prognostic biomarker). In FTD, a number of biomarkers are being used clinically and in a research capacity including MRI (both qualitative and quantitative), PET, SPECT, neurophysiology (EEG and ERP), biological markers from CSF, and finally genetic analysis.

Brain Imaging

Brain atrophy is one of the cardinal features of all neurodegenerative processes, even if it occurs at vastly different rates and by vastly different and sometimes convoluted processes. The most convincing hypothesis underlying the atrophic process is that we can no longer think of this as a generalized shrinkage but more along the lines of a Wallerian degeneration constrained by neuronal and functional networks. The process often starts focally and spreads along these networks whose predictability gives us the clinical phenotypes we know.

MRI

Brain imaging is an essential and routine examination in any dementia to exclude alternative pathology and aid in the diagnostic process. T1-weighted magnetic resonance imaging is the method of choice for evaluation of structural changes in the brain. In particular, the addition of coronal imaging to the standard axial slicing allows for the detection of visually obvious atrophy in frontal and temporal regions. T2-weighted imaging usually using fluid-attenuated sequences (FLAIR) allows for the evaluation pathology that might exclude FTD or point to a mimic syndrome such as vascular-related white matter pathology. Quantitative MRI is generally a research tool and embodies the three main techniques: volumetric analysis of specific brain regions, voxel-based morphometry (VBM), and serial co-registration.

Typical Brain Imaging Findings in FTD

Bv-FTD. Brain atrophy on static MRI is the most reproducible features of all FTD subtypes and the capacity to identify this reliably is limited in the clinic to the experience and expectations of the observers (Fig. 6.4a). In research work, serial co-registration, region of interest, volumetric analysis, and VBM have provided a key dimension to the analysis of the in vivo brain and it is an important challenge to improve these techniques to allow their routine use in clinical situations. The presence of true focal atrophy has a high positive predicative value for clinical dementia. On the other hand, the absence of atrophy has been noted increasingly in cases deemed to have all clinical, behavioral, and neuropsychological

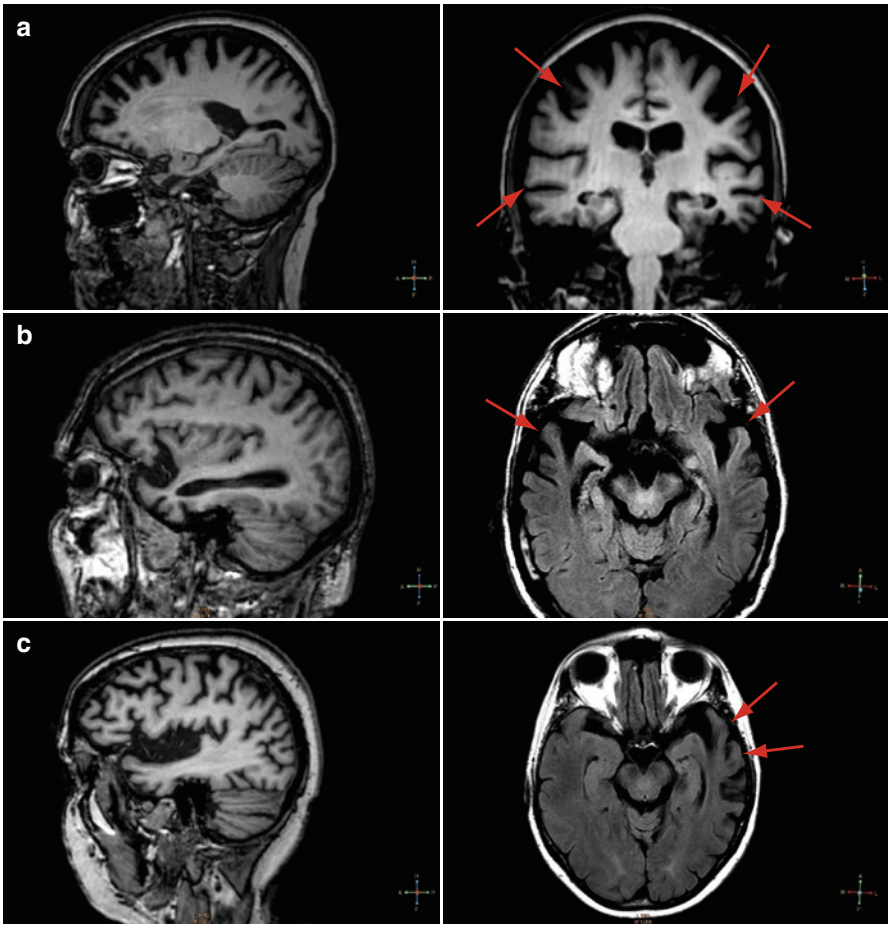

Fig. 6.4 (**a**) Behavioral variant FTD. Note generalized atrophy in frontal and temporal regions (*arrows*) with slight asymmetry favoring more atrophy on the left. (**b**) Semantic dementia. Note anterior temporal tip atrophy bilaterally (*arrows*). (**c**) Progressive nonfluent aphasia. Note asymmetric atrophy favoring the left temproal lobe (*arrows*)

features of bv-FTD. This raises the question of either a behavioral phenocopy of FTD or else cases where atrophy is either negligible or will occur later in the disorder.

On standard MRI, specific asymmetric lobar atrophy in the frontal regions with or without temporal atrophy is the best predictor of the bv-FTD subtype. Recent research has shown that the process starts in the orbitofrontal and cingulate regions and spreads to insular cortex and thence to the basal ganglia. Using functional techniques, hypoperfusion of frontal regions in SPECT has been shown to be sensitive but not specific for bv-FTD, although again asymmetry of perfusion of the frontal regions using either PET or SPECT in individual cases, especially where there does not appear to be much atrophy, improves the specificity. In research, PET studies have tended to show generalized hypometabolism but most significant in the mesial frontal regions consistent with the focal onset of many bv-FTD patients. This finding has been enhanced by a series of VBM-based studies that have pointed to regional sites within the mesial frontal zones that correlated with specific behavioral manifestations such as apathy (frontal pole), disinhibition (subcallosal region), and abnormal motor control (dorsal medial atrophy).

SD. MRI findings in SD tend to be more consistent (Fig. 6.4b). Cases typically have focal anterior temporal pole atrophy with involvement of the inferior surface (especially the fusiform gyrus) more than superior. The atrophy is typically bilateral but asymmetric cases of predominantly left-sided atrophy are more common than those with predominantly right-sided atrophy, for reasons that are unclear. In addition, a variable amount of frontal atrophy is almost always found in these cases. Functional imaging does not usually add anything in the clinical setting, with dramatic hypometabolism evident in the regions of the anterior temporal lobes that are almost universally affected by regional atrophy.

It is clear that while atrophy maybe widespread in both frontal and temporal lobes as in other cases of FTD, it is the predominance of the anterior and inferior temporal lobe atrophy findings that appear to correlate with the main clinical findings in SD. Loss of ability to form semantic word associations correlates most strongly with damage in the region of the left anterior fusiform gyrus.

PNFA. Imaging findings in PFNA are less reliable than in either bv-FTD or SD, but most MRI studies report predominant involvement of the left hemisphere, specifically atrophy of the perisylvian fissure, inferior frontal lobe, anterior insula, and basal ganglia (Fig. 6.4c). In studies of functional imaging such as PET, the abnormal findings are also widely distributed but tend to focus on the left frontal regions. In PNFA-G, imaging findings using VBM have found atrophy in the region of the first frontal convolution (Broca's area). In PNFA-L, VBM findings have shown abnormalities further back than in the agrammatic form with the angular and supramarginal gyrus and other posterior perisylvian regions involved.

Neurophysiology

Electroencephalography

The use of EEG in dementia was more widespread before the advent of brain imaging but even then its clinical and diagnostic use was limited. There is a tendency for the background

organization features of the EEG to be preserved in FTD whereas in AD, the emergence of background slowing is common as the disease progresses. The reasons for such preservation in FTD are unclear but the observation may reflect the relatively rare association between FTD and seizures compared to AD. In the research lab, quantitative EEG (qEEG), which is a digital algorithm of the different wave frequencies, has tended to confirm the preservation of resting alpha rhythm but the loss of some faster frequencies in the beta range. Further work in this area is required before EEG is to be considered a useful biomarker.

Electromyography

Because of the coexistence of ALS/MND and FTD, EMG has become an important diagnostic tool in young-onset dementia that have associated motor or swallowing difficulties (see Chap. 7). As yet, the status of EMG as a biomarker is unclear, as the use of EMG in unselected FTD cohort is not likely to be either cost-effective or clinically valuable.

CSF

Cerebrospinal biomarkers in FTD remain elusive but hope remains for a breakthrough in the next few years. Progress in CSF biomarkers in AD (total tau measurement, hyperphosphorylated tau and Aβ(beta) (1–42) has not been mirrored in FTD (see Chap. 3). The most obvious reason for this is the pathological heterogeneity of FTD compared to AD. For obvious reasons, measuring tau is unlikely to be of value in so-called tau negative ubiquitin-positive pathological subtypes. The situation is not helped by the overlap between clinical and pathological phenotypes such that any of the three major subdivisions of FTD – bv-FTD, SD, or PNFA – could eventually prove to have either tau-positive or ubiquitin-positive inclusions. The exceptions to this general rule are CBD, which is usually a tauopathy and FTD/ALS, which is generally positive for TDP-43. Finally, there is the problem FTD phenocopies, which may include normal brains and also AD, which may present as a PNFA, particularly of the logopenic variant (see Chap. 3). While it fails to clearly differentiate between AD and FTD, there is a confluence of research that shows a reduction in Aβ(beta) 1–42 as is seen in AD.

Neuropathology of FTD

The neuropathology associated with the clinical entities of FTD (bv-FTD, PNFA, SD) is heterogeneous with the common feature being a relatively selective degeneration of the frontal and temporal lobes. As in other neurodegenerative conditions, most pathological subtypes of FTD are characterized by specific kinds of intracellular protein inclusions. In the past few decades, the biochemical composition of many of these inclusion bodies has been determined. There is a growing trend to classify FTD based

on the presumed molecular defect. This is because it is thought that the molecular defect most closely reflects the underlying pathogenic process and because many of the eponymous and descriptively named syndromes of the past are now known to have imperfect clinicopathological correlation. Table 6.5 summarizes the timeline of FTD discovery over the last 100 years.

Table 6.5 Timeline of discoveries in the molecular pathology of FTD

Year	Event
1892	Arnold Pick describes patients with progressive impairment of behavior and language.
1911	Alois Alzheimer describes macroscopically, atrophy of frontal and anterior temporal lobes and microscopically; round silver impregnated inclusions and swollen neuronal perikarya (cell bodies) in the brains of these patients.
1927	Schneider calls these cells Pick bodies, the defining histopathological lesion of Pick's disease.
1939	Sander describes large pedigree (Dutch Family 2) of autosomal dominant dementing disorder characterized by behavioral disturbance, disinhibition, language disturbance, and hyperorality. Locus for this family found in 1997 (see below).
1987	Gustafson (Lund) describes frontal lobe degeneration of non-Alzheimer type.
1996	Snowden (Manchester) describes similar descriptions called frontotemporal lobar degeneration. Both groups collaborated on the first consensus criteria the so-called Lund-Manchester Criteria for frontotemporal dementia (FTD).
1994–1996	Two separate kindreds of dementia with parkinsonian features are linked to locus *Chr 17q21–22.* Dutch family 2 linked here in 1997 and at least 13 other families linked soon thereafter. Neurons with tau inclusions (see Fig. 6.5a) linked the neuropathology of the Chr 17q families with FTD with or without parkinsonism (FTD17-T or FDTP17-T), which is the region that includes the gene for tau (MAPT). Since then, 44 mutations in MAPT have been described in families with FTD17-T.
2000	Several reports of families with non-Alzheimer dementia with ubiquitin-positive but tau-negative pathology mapped to the same region of Chr 17 (see Fig. 6.5b).
2006	A number of research groups show mutations in the *progranulin gene* (*GRN*), a gene located on Chr 17 very close to MAPT (FTD17-U). To date, 68 mutations in PGRN have been found in FTD17-U families. TAR DNA binding protein (TDP-43) identified as the major component of ubiquitinated inclusions in FTD17-U. FTD17-U with TDP-43 is the major pathology in FTD/ALS.
2004–2006	In 2004, a series of mutations in the gene encoding *valosin-containing protein* (*VCP*) are found to cause a rare condition of FTD, inclusion body myocytis and Paget's disease of bone. Mutations in the gene (TARDBP) encoding TDP-43 have been found in ALS, ALS/FTD and, rarely, in FTD alone. Also, in 2005, mutations in *charged multivesicular body protein 2b CHMP2B* gene on Chromosome 3 were found to cause a familial FTD first identified in Jutland in 1980s.
2009	*FUS* (*fused in sarcoma*) protein identified as protein in some FTD17-U, TDP-43 negative inclusions. Mutations in FUS gene have been found in familial ALS and, more recently, in FTD without ALS.

Common Features

The most common gross neuropathological finding is focal, often asymmetric, lobar atrophy of the frontal lobe, and/or temporal lobes with microscopic neuronal loss in the superficial laminae of the cortex. Importantly, normal brain imaging studies do not exclude microscopic FTD pathology. Crucially also is the observation that pathological subtypes of FTD do not map onto clinical features in a one-to-one manner. The association of a highly specific constellation of symptoms and signs with a variety of neuropathological findings may seem paradoxical but may be understood in terms of systems neurodegeneration, .i.e., degeneration of neuronal populations that are connected structurally and functionally.

In 1911, Alois Alzheimer described round silver-impregnated inclusions and swollen neuronal perikarya (cell bodies) in cases of dementia with prominent language and behavioral symptoms, first described clinically by Arnold Pick in 1892. The inclusions would become known as Pick bodies, the defining histopathological lesion of Pick's disease. After a period where little progress was made beyond those original descriptions, renewed interest in the family of non-Alzheimer dementias with prominent frontal and temporal atrophy showed that only minority had classic Pick-type pathology. In the last 30 years, significant progress in descriptions of the pathological subtypes has been made.

Pathological Subtypes

Recent advances in molecular genetics, biochemistry, and neuropathology of FTD prompted the Midwest Consortium for Frontotemporal (Lobar) Degeneration and other groups to review and revise the existing neuropathological diagnostic criteria for FTD. The proposed criteria for FTD are based on existing criteria, which include:

The Tauopathies

Tau is a microtubule-associated phosphoprotein that binds to tubulin and stabilizes the cytoskeletal structures of axonal transport. Tau staining can be demonstrated in the following; FTD with pick bodies, CBD, PSP, sporadic multiple system tauopathy with dementia, argyrophilic grain disease, neurofibrillary tangle dementia, and FTD with microtubule-associated tau (MAPT) gene mutation, also called FTD with parkinsonism linked to chromosome 17 (FTDP-17) (see below). Abnormal tau aggregates that are seen not only in FTD, CBD, and PSP but also in AD provide a toxic gain of function mechanism for neurodegeneration. The microscopic appearance of the cortex shows loss of neurons, widespread spongiosis, and astrocytosis obscuring normal pathology. Pick bodies as originally described by Alzheimer are now known to be spherical cytoplasmic inclusions that are tau positive. Pick bodies are typically found in the cingulated gyrus, insula, inferior parietal lobule, and inferior temporal gyri. They are also found in the mesial structures, particularly the granule cells of the dentate fascia (Fig. 6.5a). White matter pick bodies are more common in CBD and PSP but can be found in FTD. Pick bodies may also be found in the basal ganglia and substantia nigra.

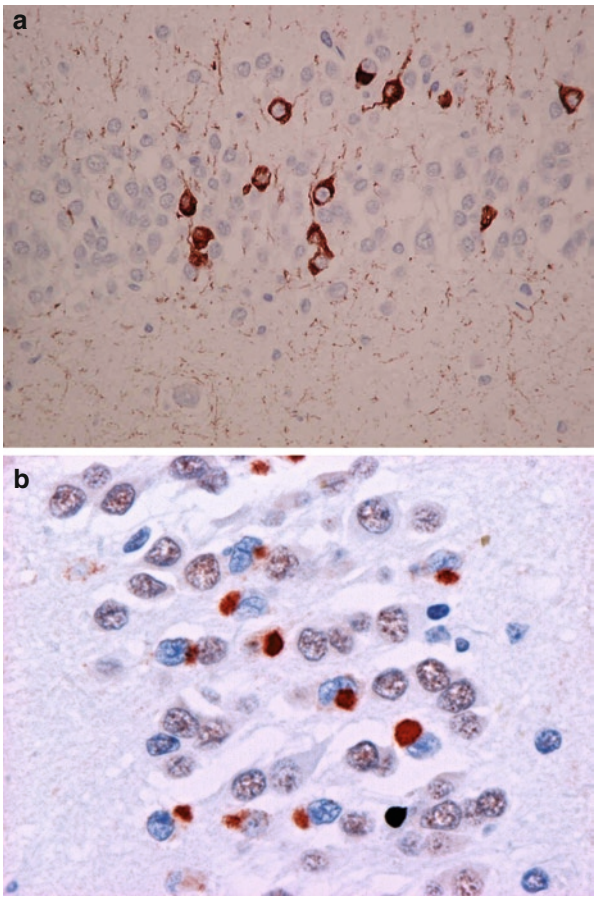

Fig. 6.5 Microscopic staining in FTD. (**a**) Tau-positive staining in FTD17-T (*arrow*) (Courtesy Prof. Michael Farrell); (**b**) TDP-43 staining in FTD-U/ALS (*arrow*) (Courtesy Prof. Ian R. A. Mackenzie)

Ubiquitin Positive (Tau-Negative) Pathology

This is now understood to be the most commonly found pathology in FTD. In 2004, the first ubiquitin protein was identified in an FTD phenotype as intermediate filament in a disorder known as neuronal intermediate filament inclusion disease (NIFID). In the majority of cases, however, the ubiquitinated inclusions contain a protein called TDP-43 (FTD-TDP).There are four subtypes of this type of pathology described in the recent consensus criteria by Cairns et al:

- Type 1 with neurites predominantly.
- Type 2 with cytoplasmic inclusions predominantly.
- Type 3 with intranuclear inclusions.
- Type 4 associated with VCP mutations (see below).

Recently, other non-TDP-43 proteins have been identified as in ubiquitin-positive, tau-negative cases. About 10% of cases have been shown to stain positively for the FUS (fused

in sarcoma) protein, although these are not due to FUS gene mutations. A smaller number that are IF-, FUS-, and TDP-43 negative have mutations in the CHMP2B gene (see below).

Microscopically, brains with TDP-43 inclusions show neuronal loss, microvacuolation, and gliosis of superficial cortical laminae. There may be loss of brainstem and spinal motor neurons with astrocytosis as can be seen in classical ALS. The defining lesion is the ubiquitin-positive cytoplasmic inclusion found in neurons in the granule cell of the hippocampal dentate fascia and in the superficial cortical layers (Fig. 6.5b).

Dementia Lacking Distinctive Histology

This is a rare and controversial entity – new analyses have allowed many cases to be reclassified into one of the positively defined subgroups above.

Genetics

Introduction

The progress in this area, moribund for decades despite the recognition of the importance of heritability since the 1920s, has been rapid and ever-expanding.

Distinguishing Sporadic and Genetic Forms of FTD

The traditional disease dichotomy of "sporadic" versus "genetic" is still used but is increasingly difficult to support, due to the likely polygenic factors influencing sporadic FTD. Nevertheless, the first step in determining whether there is a genetic influence in a disorder is to establish the frequency of a family history of the disorder.

At the clinical epidemiology level, the accuracy of ascertainment of familial disease is confounded by informant reliability, the late onset of the disease, and the possibility of death before disease expression, and the variable phenotype of FTD-related diseases. The earliest well-documented large pedigree was first reported in 1939 by Sanders and colleagues, who described an autosomal dominant dementing disorder with behavioral and cognitive disturbances with relative preserved memory, affecting a Dutch kindred known as Dutch family 2. However, the earliest estimates of the frequency of family history came from the Lund and Manchester clinicopathological series, which estimated that up to 50% of patients with FTD had a first-degree relative with dementia. More recent studies have tended to corroborate this figure.

Pathological features can help discriminate familial and nonfamilial forms. Numerous mutations in the tau gene on chromosome 17 account for between 10% and 40% of familial forms. Tau positivity is therefore a strong indicator of possible genetic origin.

Conversely, tau-negative, ubiquitin-positive pathology may be the result of a progranulin mutation, which may account for up to 25% of familial forms of FTD in some populations.

Mutations in Genes Causing FTD

In chromosome-17-linked FTD families, mutations in the gene encoding the microtubule-associated protein tau (*MAPT*) and the progranulin gene (GRN) are identified. In FTD populations, the *MAPT* mutation frequency ranges from 8% to 50%, that of *GRN* from 5% to 26%. Also, mutations in the gene encoding the chromatin-modifying protein 2B (*CHMP2B*) at chromosome 3p11.2 have been identified in autosomal dominant FTD. Inclusion body myopathy with early onset Paget's disease and frontotemporal dementia (IBMPFD) was associated with mutation in the valosin-containing protein gene (*VCP*) at chromosome 9p13-p12, and amyotrophic lateral sclerosis (ALS) with FTD was linked to a locus at chromosome 9q21-q22.

Below is a description of the currently well-characterized genetic forms of FTD. A standardized way of abbreviating familial FTD has been agreed but is constantly being updated. Following FTD (also known as FTLD), a P is added if extrapyramidal parkinsonian features are present. The chromosomal linkage is hyphenated and the T is placed to indicate whether tau inclusions are seen. In tau-negative disease, U (ubiquitin proteasome system) is added after the hyphen to indicate ubiquitin staining but recently with the identification of many of the ubiquitinated proteins, the term FTD-U is now reserved for only a minority of cases.

FTD with Parkinsonism Linked to Chromosome 17: FTDP-17 T and the MTAP Gene

In adult human brain, six tau isoforms are produced from a single gene on chromosome 17 by alternative mRNA splicing. In 1994, a large Irish and American kindred was described whose genetic locus was linked to 17q21–22 where the tau gene is located. Originally known as disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC), an important clue to future dilemmas was in the clinical description: the phenotype was hugely variable. A number of other research groups linked equally diverse clinical kindreds and names such as hereditary frontotemporal dementia (HFTD), multiple system tauopathy dementia (MSTD), and pallidopontonigral dementia (PPND) emerged. Pathological features were more uniform with all studied members showing frontotemporal atrophy and tau deposition. In 1997, a consensus conference allowed for the categorization of most descriptions as "FTD with Parkinsonism linked to chromosome 17." Most recently, it has become clear that such widely varying clinical syndromes such as PSP, CBD, and FTD can coexist within families with MAPT mutations.

The age of onset of FTDP-17 is between 30 and 65 years. Behavioral and cognitive problems predominate and memory and praxis are relatively preserved. By definition, most have prominent parkinsonian features and amyotrophy is rare.

To date, 44 mutations in MAPT in 132 kindreds have been described. Most coding mutations occur in the microtubule binding repeat region or very close to it. These potentially lead to a partial loss of function of tau with reduced tau binding to microtubules.

FTD Linked to Chromosome 17: FTD-17TDP the Progranulin Gene and the Valocin-Containing Protein Gene

In 2000, several pedigrees linked to chromosome 17 were identified without MAPT mutations but with typical ubiquitin-positive, tau-negative inclusions. In 2006, several research groups described a serious of mutations in the GRN gene. To date, 68 mutations in 210 families have been found. The average age of onset of dementia in progranulin families is the sixties with the clinical spectrum encompassing apathy, typical cognitive features of FTD, and some with FTD/MND (see below). Progranulin is associated with tumorigenesis when overproduced; however, the mutations seen in GRN associated with FTD are associated with reduced circulating levels of progranulin.

Because progranulin is not incorporated into ubiquitinated inclusions, a search for the FTD-U disease protein was undertaken and in 2006 an international research team identified the protein as TAR DNA binding protein, also known as TARDBP or as TDP-43. This cellular protein is encoded by the TARDBP on chromosome 1. This protein was originally identified in the brains of patients with FTD/ALS but it is now known to be the major protein in FTD-17U and has been termed FTD-TDP; four subtypes have recently been identified. Type four has been associated with brain pathology seen in a small number of cases of FTD combined with inclusion body myositis and Paget's disease of bone. Four families with this condition linked to the short arm of chromosome 9, and in 2004 a series of mutations in a valosin-containing protein (VCP) were found. To date, 13 mutations have been found in 30 families.

FTD with Motor Neuron Disease

It has long been recognized that cognitive and behavioral impairment is a feature of a substantial minority of cases of ALS/MND and that some 15% reach agreed clinical criteria for FTD (see Chap. 9 for discussion). However, genes that have been described in superoxide-dismutase-related familial ALS rarely cause FTD. The pathological findings in ALS/FTD are typical of FTD-17TDP (see above), which, in non-ALS cases, have been linked to progranulin mutations with TDP-43 immunostaining. While GRN mutations have yet to be convincingly confirmed in ALS or ALS/FTD, over 31 TDP-43 gene mutations have been found in patients with both sporadic and familial ALS, and dementia has been noted in some affected kindreds.

FTD-FUS, Tau Negative and TDP-43 Negative: The FUS Protein

In 2009, international collaborators identified a subgroup of FTD patients representing about 10% of cases, with an unusual clinical phenotype and pathology characterized by

frontotemporal degeneration with neuronal inclusions composed of a ubiquitinated protein, which is TDP-43 and tau negative. All cases were of a bv-FTD phenotype with early onset (mean age of onset of 41 years), with a high prevalence of psychotic symptoms without aphasia or significant motor features. Pathology in all of these cases was characterized by positive FUS (Fused in Sarcoma) immunohistochemistry labeling of the neuronal inclusions. No actual mutations in the FUS gene were found in any of these cases.

FTD-UPS, Tau Negative, TDP-43 Negative, FUS Negative: The CHMP2B Gene

In 1984, a researcher came across a very large family in Jutland in Denmark with an unusual dementia. There were over 27 affected individuals with a very wide clinical variability. In 1995, genetic linkage to chromosome 3 was established. Since then, three kindreds have been described with mutations in a gene coding for the charged multivesicular body protein 2B (CHMP2B). The pathology is a ubiquitinated protein that is tau, TDP-43 negative, and FUS negative. More recently, a number of apparently sporadic cases with the young-onset atypical phenotype described above have been shown to have CHMP2B mutations.

There remain a small number of cases that are negative for tau, TDP-43, and FUS staining but that do not have associated CHMP2B mutations, Some of these stain for intermediate filament as in neuronal intermediate filament inclusion disease. Finally, a number of FTD-U proteins remain unidentified, suggesting that the full compliment of FTD pathologies is yet to be elucidated.

Presenilin Mutations and FTD

Recently, several families with FTD have been shown to have mutations in Presenilin1, a gene usually associated with familial Alzheimer's disease. This finding confirms the notion of convergence amongst mechanisms of neurodegeneration and is reciprocal to recent finding of MAPT polymorphisms in large AD cohorts. The exact role of presenilin in FTD is unclear

Genetics of Sporadic FTD

Despite the rapid growth in understanding of familial forms of FTD, the majority of FTD cases are sporadic, with only about 40% having a family history of dementia. However, in sporadic cases, abnormal aggregations of tau are often found, similar to that in the familial form. In the late 1990s, a series of single nucleotide polymorphisms (SNPs) in exons and flanking introns in the tau gene region, were found to be in linkage disequilibrium constituting two distinct haplotypes H1 and H2. The H1 haplotype is the most frequent seen in Caucasian populations. An association of the extended tau H1 haplotype and a number of tau-based dementias has been reported, including FTD. Furthermore, the tau H1 haplotype

increases the risk for FTD through a combined effect with Apo-E-4 and Apo-E-2 alleles. The mechanism of risk increase is unknown.

Therapy for FTD

Introduction

Currently, there are no approved disease-modifying therapies for FTD. However, the explosion in the understanding of the molecular pathology of FTD over the last decade has led to a plethora of potential targets for therapy, which have been the subject of numerous ongoing trials, some of which have competed phase III studies.

Current therapeutic management involves many approaches to symptom control and support of patient and carers.

Therapy should be based on a palliative, multidisciplinary approach to care, which should be employed from communicating the diagnosis, through managing difficult behaviors and troubling physical symptoms to the agonal stages (see also Chap. 13).

The Potential for Disease-Modifying Therapy

Therapeutic compounds for FTD have largely been drugs approved for use in other neuropsychiatric disorders including dementias such as AD. A study of memantine, an NMDA receptor antagonist approved for moderate-to-severe AD, has been shown to transiently improve the total NPI (neuropsychiatric inventory) score primarily in the bv-FTD group.

Preclinical and early clinical phase trials of true disease-modifying therapies are underway. The main targets are:

MATP in FTD with Tau Pathology

Tau is expressed in the axon of the neuron where it promotes microtubule stability. Mutations result in errors of tau splicing, cleavage, and phosphorylation. A combination of toxic gain-of-function and loss-of-function is the likely pathogenic mechanism of degeneration. Biochemical strategies for interrupting abnormal tau accumulation such as inhibiting aggregation, cleavage and expression, and interfering with splicing and stabilizing microtubules are all being explored. Immune suppression to alter abnormal tau accumulation is also under consideration.

TDP-43 in FTD-U

TDP-43 is a nuclear protein that can bind to DNA and RNA. The pathology of the inclusions seen in FTD-U is characterized by hyperphosphorylation and ubiquitination on

TDP-43, and the pathogenesis may be a mixture of gain and loss of function. Immune therapy or efforts to block cleavage may have therapeutic value in removing abnormal TDP-43.

Mutations in Progranulin Lead to Reductions in mRNA

PTC124, a new chemical entity that selectively induces ribosomal read through premature but not normal termination codons, is in preclinical trials for FTD-associated progranulin mutations.

Symptom Control and Support

Behavioral and Psychiatric Problems

A multidisciplinary approach to the range of behavior and neuropsychiatric manifestations in bv-FTD is essential. Sensitive communication of the diagnosis to patients, families, and caregivers is required. This should be done in a specialist environment with an understanding of the unique features of FTD such as the personality changes, loss of empathy, and socially embarrassing behaviors. A range of therapies have been used in the last number of years to treat the behavioral manifestations of FTD. Selective serotonin reuptake inhibitors have been amongst the most widely studied drugs and now considered first-line treatments. Memantine has shown promise (see above) but placebo-controlled trails are awaited. Finally, atypical antipsychotic agents such as quetiapine may be considered for treatment of agitation, delusions, and aggression.

Cognitive Impairment

There are no approved therapies for cognitive impairment. Acetylcholinesterase inhibitors, widely used in mild-to-moderate AD, may worsen behavioral symptoms in FTD. Neuropsychological strategies can help patients and caregivers cope with the worst effect of cognitive impairment.

Speech and Language Therapy

Speech and language therapy in PNFA may offer some benefit to patients early in the course of the illness, as does utilization of communication aids by caregivers.

Sleep

Sleep disturbances should be managed by maintaining a regular sleep regime and may be aided by the use of the sedating antidepressant Trazodone. With altered dietary behaviors and weight gain, obstructive sleep apnea may become a problem and can be responsible for sudden worsening of cognitive function.

Motor Impairment

Parkinsonism and amyotrophy are the most common motor manifestations of advanced FTD and approaches to managing these aspects of the disorder are dealt with in Chaps. 5 and 7.

Incontinence

Prominence of early bladder difficulty should give rise to suspicion of disorders of autonomic control such as PSP rather than FTD. However, early involvement of the medial frontal lobe in both bv-FTD and CBD can lead to incontinence, which should be managed with intermittent catheterization, indwelling catheters, and the use of a leg bag or in some cased urinary diversion. The use of anticholinergics must be tempered by the possibility of increasing confusion.

Palliative Care

The inexorable decline in function and quality of life that currently follows a diagnosis of FTD should always be met with a plan for palliation and appropriate end of life care. There has been significant improvement in the knowledge and understanding of this process amongst palliative care specialists. For further discussion, see Chap. 13.

Support of Carer

It has been recognized that carers of patients with FTD report significant distress and depression even when compared to carers of patients with other forms of dementia. This is most likely due to the FTD patient's behavioral dysfunction and poor social cognition. The multidisciplinary team should be aware of these stressors on the carer. Support to the carer can be provided through advice and instruction on how to manage disruptive behavior, and the availability of respite care.

Significant Advances in the Past 5 Years and a Look to the Future

Phenotypic Variability and Clinical Presentation

Frontotemporal dementia is remarkable for the striking variability in clinical presentation and, as has become more evident in recent years, heterogeneity in the underlying patterns of brain atrophy, the latter, to a large extent, accounting for the former. Apart from the original prototypic behavioral and aphasic (fluent and nonfluent) forms pronounced apathy has been associated with dorsolateral and medial frontal lobe atrophy, disinhibition with orbitofrontal and temporal lobe changes, and a variety of behavioral features specifically with the right temporal lobe. Distinct anatomical subtypes of

behavioral variant FTD have been identified, including frontal-dominant subtype, temporal-dominant subtype, and frontotemporal and temporofrontoparietal subtypes.

Furthermore, it has been an assumption that FTD is not a dementia of old age, yet a prevalence rate of 3% has been reported for bv-FTD in 85 year olds. There has also been a growing literature in relation to distinguishing between true FTD and behavioral phenocopies, with implications for differential diagnosis, prognosis, and possible intervention. There have also been huge strides in elucidating the major overlap that exists between FTD and conditions with which it was not initially associated, including ALS, CBD, and PSP.

Neuropsychology

It has become evident that some of the features that were originally believed to be defining characteristics of FTD require clarification. For example, early severe memory impairment has generally been considered to contraindicate FTD, but in fact, severe amnesia can be a presenting feature in a few cases. In a similar vein, prominent psychotic features are not anticipated in FTD, but recent studies show that in some cases a schizophrenia-like psychosis can present several years before the emergence of more obvious FTD. Progress has also been made in developing novel tools to investigate distinctive features of FTD such as breakdown in social judgement, decision making, empathy, and emotion processing, with implications both for differential diagnosis and for understanding the anatomical substrates of higher order cognition, emotion, and social behavior. New diagnostic criteria will emerge soon, which are based on a greater understanding of the types of behavior change manifest and interaction with dysfunction in social cognition. Moreover, the relationship of FTD and MND has evolved with the demonstration of a spectrum of cognitive impairment in these disorders and with a possible subclinical FTD syndrome in a large number of MND cases.

Biomarkers

Brain Imaging

Advances in brain imaging have grown at a remarkable pace in the last 5 years. Specific pattern of lobar atrophy can now be reliably mapped to clinical phenotypes. Indeed, some have argued that the presence of atrophy of the polar regions of the temporal lobe along with the fusiform gyrus are so reliable that they should form part of the diagnostic criteria at least for SD, with patterns in other subtypes not far behind in terms of reliability. A key challenge for the future is to try and improve the automation of computer-aided quantitation of MRI such that techniques such as VBM and DTI can be of use diagnostically at the individual patient level. The advent of 3 T MR imaging with double the field strength and four times the resolution as a standard clinical imaging modality will go hand in hand with the addition of the automated techniques to improve diagnostic accuracy. Finally, the role of functional imaging has yet to be fully elucidated and there is an urgent requirement for

a protein ligand that can reliably detect abnormal pathology in FTD similar to the discovery of Pittsburgh Compound B (PIB), which detects the presence of amyloid in the brain (see Chap. 3).

Blood and CSF Biomarkers

Detection of low or high levels of tau, progranulin, or TDP-43 are the holy grail of biomarker research in FTD since they would be conforming with key elements of what is already known about the molecular pathogenesis. To date, such biomarkers remain elusive. For the moment, the consistent finding of lower levels of Aβ(beta) 1–42 similar to that in AD has yet to be explained. Recently, a subgroup of FTD patients has been shown to have remarkably high CSF levels of both light chain and hyperphosphorylated heavy chain neurofilaments (NfL and NfH). The degree of NfH phosphorylation is increased in FTD compared to both AD and controls. The pathological significance of these neurofilaments remains to be determined. Finally, the search for novel biomarkers has involved the use sophisticated mass spectroscopy. Among candidates that have been found are the neurosecretory protein VGF, transthyretin, S-cysteinylated transthyretin, truncated cystatin C, and a fragment of chromogranin B.

Molecular Pathology

Improvements in assays of the functional effects of the tau mutations may enable us to link the size of molecular effects to the severity of the clinical phenotype. It already seems likely that a large effect on microtubule-binding and tau aggregation equates to a more severe phenotype. In addition, the exon-10 splice site mutations appear to correlate with clinical phenotype based on the degree to which they disrupt splicing.

Future Advances in Treatment

Treatment for FTD, a condition for which there was at best a small range of drugs for symptom control available until recently, has advanced hugely. The development of multidisciplinary clinical teams for diagnosis and follow-up has brought a range of expertise to bear on the difficult problems that this dementia of predominantly young people with families brings. Clinical nurse specialists, clinical psychologists, speech therapist, social workers, physiotherapists, and palliative care specialists along with neurologists with a special interest in cognitive neurology all have a role to play in both patient and caregiver support. The enhancements provided by teams of this type are aided by the use of a range of pharmacological therapies for symptom control.

The goal for the next 5 years, however, is to find the elusive disease-modifying therapy that can give hope to the afflicted and to the many families concerned for the future of children and relatives of those with a disease with a highly likelihood of familial disposition. The advances in the understanding of the neuropathology and molecular pathology of

FTD have thrown up tantalizing targets for therapy. Studies on the interruption of the deposition of abnormal tau are ongoing and will undoubtedly lead to approved treatments for both AD and FTD. Treatments directed against other targets such as progranulin and TDP-43 will not be far behind.

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