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# FRONTOTEMPORAL DEMENTIA (FTD) 2011

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## SUMMARY

Arnold Pick's description of lobar atrophy with progressive aphasia, apraxia and behavioural disturbance has been re-named Frontotemporal Dementia (FTD). A significant expansion of knowledge has occurred in the last few years, especially in the molecular biology of FTD, which is estimated to account for 12-15% of all dementias and 30-50% of early onset cases. The clinical picture consists mainly of behavioural and language impairment, but the extrapyramidal syndromes of Corticobasal Degeneration (CBD) and Progressive Supranuclear Palsy (PSP) also belong to the FTD family. Indifference, disinhibition and hyperorality are characteristic of the commonest, behavioural variety. Progressive aphasia is equally characteristic, either agrammatic and nonfluent or anomia and semantic type. Sometimes motor neurone disease is associated. The current terms in use are: behavioral variant FTD (bvFTD), the nonfluent variety of Primary Progressive Aphasia (nfvPPA), the logopenic variety (lvPPA), and semantic dementia (svPPA). These different presentations converge, as various areas in the brain are affected. Less than half of the cases are tauopathies, the majority have been discovered to have ubiquitin inclusions: a TDP-43, and most recently an FUS proteinopathy, shared with ALS, opening potential opportunities for pharmacological approaches to treatment. The high familial incidence, with tau and progranulin mutations on Ch-17 and some others, point to a molecular, genetic etiology.

## INTRODUCTION

Frontotemporal dementia (FTD) is the current name for clinical Pick's disease (PiD). The eponymic term may be preferable because its obvious symmetry to Alzheimer's disease (AD), and for historical accuracy. Many caregivers object to the term "Dementia" and Frontotemporal Disease is beginning to be used instead. Arnold Pick described the clinical picture of frontotemporal atrophy more than a century ago (Pick, 1892). Pick's initial case of a progressive aphasic patient with behavioral disturbances had only gross examination without any microscopic data, but the clinical description and its relationship to focal atrophy is the basis of the syndrome. Pick also linked several cases of focal atrophy of the left temporal lobe with a clinical picture of word deafness, similar to what is currently referred to as "semantic dementia" (Pick, 1905). Some patients presented with amnesic aphasia and had word deafness only at the later stages. In this paper he suggested the clinical complexity: "cases with temporal atrophy show ab initio clinical differences, even if later they tend to converge and look identical." Later, PiD was defined on the basis of round silver staining inclusions, initially described by Alzheimer (Alzheimer, 1911). Frontotemporal atrophy was demonstrated later in vivo, first with CT and later with MRI and SPECT. However, instead of shifting the diagnosis of PiD back to the clinic, several studies applied new labels such as frontal lobe degeneration (FLD) (Brun, 1987) or dementia of the frontal lobe type (Neary et al., 1988), and subsequently frontotemporal dementia (FTD) (Brun et al., 1994). These terms were initially applied mainly for the behavioral presentation. The aphasic presentation was described as Primary Progressive Aphasia (PPA) (Mesulam, 1987), the extrapyramidal component as Progressive Supranuclear Palsy (PSP) (Steele et al., 1964) or Corticobasal Degeneration (CBD) (Gibb et al., 1989). Recently these were recognized as being different presentations with clinical, pathological and biological overlap. Since FTD is used for both the overall disease and the behavioral presentation ambiguously, the term "Pick complex" (PC) was suggested to encompass all the related entities both clinically and pathologically (Kertesz et al., 1994). Others have used "frontotemporal lobar degeneration" (FTLD) (Snowden et al., 1996), and this term is the one used by pathologists with qualifier letters to denote the underlying proteinopathy such as FTLD-T for tauopathy or FTLD-U for Ubiquinopathy (Cairns et al., 2007).

### ***Behavioral Variant Frontotemporal Disease – (bvFTD)***

The predominantly behavioral changes often begin with apathy and disinterest, which may be mistaken for depression. On the other hand, the symptoms of disinhibition may suggest a manic psychosis or an obsessive-compulsive or a sociopathic personality disorder (Gregory & Hodges, 1996; Miller, Darby & Benson, 1997). The initial syndrome may be only a deficit of executive function, such as the inability to plan or carry out complex tasks. The patient may be inattentive, impulsive, and distractible. When the striking disinhibition and asocial behavior appear, the diagnosis is unmistakable, but neuroimaging is essential to exclude

neoplasm. Childish behaviour, rudeness, inappropriate sexual remarks, impatient, careless driving, excessive spending or hoarding of certain items, inappropriate joking, perseverative routines, compulsive roaming, insistence on certain foods, excessive food intake, neglect of personal hygiene, disinterest in the immediate family or others are the most characteristic features (Miller, Darby & Swartz, 1995). The personality change often prompts the family to say that the patient is not the same person any more. Pilfering, shoplifting, swearing, undressing in public, unexpected urinary and fecal incontinence rapidly bring the patient to the physician, sometimes after the police are involved.

The symptom pattern is known to physicians familiar with frontal tumors, lobectomies, and trauma ever since the classic description of Phineas Gage, a conscientious, reliable, hard-working foreman, who became irresponsible, ill-mannered, indifferent, and incompetent, after a tamping iron had blown through his frontal lobes. Harlow, his physician, commented on the change of personality: "Gage was no Gage any more." Some of the more advanced behavioral syndromes of FTD resemble the so-called Klüver-Bucy syndrome (Cummings & Duchon, 1981), which is produced in monkeys by bilateral ablation of the temporal lobes and can be seen in humans after encephalitis. The syndrome consists of hyperorality (placing objects in the mouth, or excessively eating anything), hypersexuality (mostly words and gestures), compulsive touching (also called utilization behavior), and disinhibited exploration of the environment (roaming).

Neuropsychological deficits have been variable because of the types and methods of patient selection at different stages of illness and the tests used (Miller et al., 1991; Hodges et al., 1999). The Mini-Mental State Examination (MMSE) may be normal in early cases. Orientation and episodic memory are relatively preserved. Frontal lobe functions are impaired, although some patients with behavioural presentation perform well on "frontal" tests, especially if they are seen early. Although FTD can present as a subtle "executive" impairment, executive deficits are often involved in AD as well. There may be a memory complaint in FTD, but impaired memory performance could result from inattention, lack of motivation, and/or language impairment. Although drawings in FTD patients may be impoverished due to amotivational performance, visuospatial function is generally intact. Some patients may be perseverative in drawing. At times copying can be compulsively faithful to detail. Visuospatial tasks, that tap executive function, such as trail-making, are impaired at an early stage, but performance on block design and Raven's Coloured Progressive Matrices may be preserved. At times, impulsivity, disinhibition, perseveration, echopraxia, and utilization behavior are observed during neuropsychological testing. In later stages the patient may be too restless or language impaired to test.

The caregiver's history and responses to a questionnaire, such as the Frontal Behavioral Inventory (Kertesz et al., 2003), at the initial interview are the most useful diagnostic tools. The inventory was designed as a series of structured questions scripted so that both the normal and abnormal aspects of the behaviors were included. Each item was scored on a scale of 4, where 0 = none, 1 = mild or occa-

sional, 2 = moderate, 3 = severe or most of the time. The first group of items are negative behaviors, such as apathy, asponaneity, indifference, inflexibility, concreteness, personal neglect, distractibility, inattention, loss of insight, logopenia, verbal apraxia, and alien hand. These last three items were included to capture specific motor and speech behaviors, which may be associated with FTD. The second group of items contains disinhibited behaviors, such as perseveration, irritability, jocularity, irresponsibility, inappropriateness, impulsivity, restlessness, aggression, and hyperorality. A score above 27 is cutoff for bvFTD. We demonstrated that using cognitive tests alone was only 75% accurate in distinguishing FTD from AD patients, while adding FBI to the discriminant function achieved 100% discrimination.

### ***Primary Progressive Aphasia (PPA)***

Although aphasia with circumscribed frontotemporal atrophy was described by Pick almost a century before, it was redescribed as primary progressive aphasia (PPA) by Mesulam (1987). Variations of this terminology—particularly progressive nonfluent aphasia (Grossman et al., 1996) and progressive aphemia have been used. The condition was considered a separate entity for a while, but evidence has been presented to consider it part of Pick complex/FTD (Kertesz et al., 1994). The further fractionation to nonfluent, fluent, and logopenic varieties is a recent development (Gorno-Tempini et al., 2004). The logopenic variety overlaps with AD (Mesulam et al., 2008). The initial presentation of PPA is often word finding difficulty, or anomia. In this respect, PPA patients are not much different from Alzheimer patients, except they have relatively preserved memory and nonverbal cognition. AD patients, by the time they show aphasic difficulty, already have significant memory loss, disorientation, and visuospatial impairment. The relatively isolated language disturbance in the first two years of the illness was suggested by Weintraub and Mesulam (1990) as the operational definition of PPA. However, many cases have behavioral or extra-pyramidal features, which appear before the two years into the illness. Some patients present with stuttering or slow, segmented speech and verbal apraxia, which includes articulatory difficulty and phonological paraphasias (Josephs et al., 2006). Progressive limb apraxia can be a prominent feature (Fukui et al., 1996), indicating a clinical overlap between PPA and the apraxic-extrapyramidal syndrome of CBD. Comprehension and nonverbal intelligence and episodic memory are maintained (Karbe et al., 1993; Weintraub et al., 1990). The course is variable and may be considerably prolonged, but sometimes patients who develop pathology in the basal ganglia or motor neuron disease progress quickly and develop difficulty with swallowing and choking. Mutism has been considered characteristic of PiD, and it tends to be the end-stage of all forms of FTD, even those that start with behavioral abnormalities rather than language disturbance. End-stage mutism also occurs in AD, but usually in a patient who already has global dementia with loss of comprehension and basic functions of daily living. In FTD and PPA mutism occurs with relative preservation of comprehension, unlike in global aphasia or in severe AD.

### ***Semantic Dementia (Aphasia)***

A distinct variety has been described as “semantic dementia” (Snowden et al., 1989). These patients progressively lose the meaning of words, but retain fluency and are able to carry out a conversation. Subsequent descriptions of this entity adopted this term (Hodges et al., 1992), and more recently it has been used extensively. The picture is similar to “transcortical sensory aphasia,” in which articulation, repetition, phonology and syntax remain intact but the patient does not comprehend well and cannot name objects. Typically they ask the meaning of nouns in conversation, with “What is...?” questions (Kertesz et al., 2010). Initially such patients produce semantic substitutions and later fluent semantic jargon, often totally irrelevant to the questions asked or the topics discussed. Patients with semantic dementia differ significantly from the fluent aphasics of AD because they have a relatively preserved episodic and autobiographical memory. Semantic dementia is often associated with bvFTD, and patients who present with the behavioral symptoms often have elements of semantic dementia (Pachalska et al 2011).

### ***Corticobasal Degeneration/PSP***

Prominent extra-pyramidal features in PiD have been observed for some time (Akelaitis 1944). Sometimes unilateral rigidity and Parkinsonism are the first symptoms to attract attention. It has long been recognized that subcortical changes occur in PiD, even without extrapyramidal symptomatology (Munoz-Garcia & Ludwin, 1984).

When Rebeiz et al. (1968) described corticodentatonigral degeneration, they recognized the similarity of the pathology to PiD. The clinical syndrome of unilateral rigidity, prominent apraxia, gaze palsy, reflex myoclonus, and the alien hand syndrome was relabelled corticobasal degeneration or corticobasal ganglionic degeneration (Gibb et al., 1989). Some case reports have described patients with clinical features of CBD as defined by unilateral rigidity, apraxia and alien hand syndrome, but also the pathological findings of PiD with Pick bodies (Lang et al., 1992). Other cases pathologically typical of CBD have had FTD or PPA without the extrapyramidal features (Lippa et al., 1990). We suggested that the clinical syndrome of prominent apraxia, unilateral extra-pyramidal syndrome, and alien hand phenomenon should be designated as corticobasal degeneration syndrome (CBDS), and CBD should be used for the pathological picture (Kertesz & Munoz, 1998). CBDS and PSP have shown significant overlap with the syndromes of FTD/Pick complex (Kertesz et al., 2000).

The syndrome of axial dystonia, bradykinesia, falls, dysphagia, and vertical gaze palsy was described as progressive supranuclear palsy (PSP) by the Toronto group of Steele et al. (1964), but the overlap with CBDS has been increasingly recognized. Many CBD patients also have vertical gaze palsy; some have falls and symmetrical extrapyramidal syndrome. Some studies comparing the neuropsychological features of PSP and CBD found no significant difference between them (Pillon et al., 1995). The pathological, biochemical, and genetic features also overlap to a great extent. They are both considered to be predom-

inantly 4 repeat tauopathies and have common tau haplotypes (Houlden et al., 2001). There is continuing controversy over to what extent PSP and CBD can be differentiated, and the evidence very much favors the conclusion that CBD/PSP is also part of the Pick complex (Josephs et al., 2006).

### ***Motor Neuron Disease and FTD (FTD-MND)***

Recently, considerable interest has been shown in the association of dementia with MND (Mitsuyama, 1984; Neary et al., 1990). Some cases of MND or amyotrophic lateral sclerosis (ALS) have FTD-like features. Beyond that, cognitive and behavioral impairment has been observed in ALS (Neary et al., 2000) and some estimate it to be as high as 50% (Lomen-Hoerth et al., 2002). It has become evident that cases of dementia with MND have ubiquitin positive, tau negative inclusions in the cortex, which have been previously described in the motor neurons in ALS (Okamoto et al., 1991). Subsequently these were also found in the majority of FTD cases without MND (FTLD-U), and most had TDP-43 proteinopathy (see below). About 10% of cases of FTD and PPA develop MND (Neary et al., 1990).

### ***Neurobiology***

The initial hallmark of the disease was the presence of Pick bodies, silver staining cellular inclusions, but these are only seen in less than 20% of cases. Later these turned out to have an underlying tau protein abnormality. Various other distinctive features, such as Pick cells (swollen achromatic neurons), astrocytic plaques in CBD, tufted astrocytes in PSP, are currently used to distinguish between varieties that are stained for abnormal tau protein (formerly silver staining), and these are commonly labelled FTLD-T (Frontotemporal Lobar Degeneration-tau), accounting for approximately 45% of FTD cases (Munoz et al. 2003; Cairns et al., 2007). The most common pathology of FTD/Pick complex turns out to have the ubiquitin positive tau negative inclusions previously described in MND (Okamoto et al., 1991). These inclusions (FTLD-U) are found on autopsy in 55% of FTD cases (Munoz et al., 2003; Lipton et al., 2004; Hodges et al., 2004; Kertesz et al., 2005).

The recent discovery of Transactive response DNA binding protein (TDP-43) in the ubiquitin positive cases of FTD as the underlying protein abnormality has changed the concept of ubiquinopathy to "TDP43-pathology" as the most common pathological and biological variety of FTD/Pick complex (Neuman et al., 2006; Mackenzie et al., 2007). Antibodies against TDP-43 have proven to be the most sensitive and specific tool to detect all of the different types of the ubiquitin positive pathology found in most cases of FTLD-U, including neuronal cytoplasmic inclusions (NCIs) and neuronal intranuclear inclusions (NIIs), suggesting that the essential nuclear functions of TDP-43 might be lost in FTLD-TDP (Neumann, Tolnay & Mackenzie, 2009).

TDP-43 protein abnormality is present in ALS and also in about 20% of Alzheimer's disease patients, so its specificity remains to be determined. Not all FTLD-U cases have the TDP-43 proteinopathy. The TDP-43 negative cases (also known as atypical FTLD-U), basophilic inclusion body disease (BIBD) and neuronal intermediate fila-

ment inclusion disease (NIFID) have been shown to have abnormal antibodies to the “fused in sarcoma” (FUS) protein (Munoz et al., 2009; Neumann et al., 2009).

The clinical varieties of Pick complex do not predict the overall pathological spectrum, but there is a prominence of tau positive CBD or Pick body pathology (FTLD-T) in the extrapyramidal and aphasic presentation, and the tau negative ubiquitin positive (FTLD-U) type with the behavioural presentation and semantic dementia (Kertesz et al., 2005).

### **Genetics**

Wilhelmsen et al. (1994) discovered linkage to chromosome 17 q21-22 in a large family with variable symptomatology of FTD, aphasia, Parkinsonism, and amyotrophy. A consensus conference summarized the clinical features of 12 families linked to chromosome 17 and the pathology, and the term *Frontotemporal Dementia with Parkinsonism linked to chromosome 17 (FTDP-17)* was accepted (Foster et al., 1997). The microtubular-associated protein tau was suspected as the candidate gene for mutation, and later several tau mutations were discovered (Spillantini et al., 1998; Hutton et al., 1998). The exon 10 splice mutations alter the ratio of 4 repeat to 3 repeat tau isoforms, most often resulting in pathology resembling CBD or PSP. Mutations in exons 9, 12, and 13 result in the predominance of 3 repeat tau and Pick body dementia.

Families with FTLD-U (MND-type inclusions, but usually without MND) have also been linked to chromosome 17, and progranulin mutations were found to account for most, but not all the familial cases, and even for some sporadic ones (Baker et al., 2006). The progranulin mutations seem to be even more frequent than the tau mutations. Progranulin is a peptide growth factor that plays important roles in mediating neuronal development, cell growth, inflammation, and wound repair, although too much progranulin has previously been linked to some cancers. The FTD patients with *PGRN* mutations, in contrast, do not produce enough functional progranulin. Such patients also have TDP-43(+) pathology at autopsy (Mackenzie, 2007). Mutations in the TDP43 protein have been described on Chromosome 1 in cases with familial ALS with or without FTD. Mutations in the FUS protein gene (see pathology section) have so far also been seen only in ALS families.

Other rare mutations in the valosin-containing protein appeared in the clinical combination of FTD with Paget’s disease and inclusion body myopathy linked to chromosome 9 (Watts et al., 2004) and a charged multivesicular protein mutation (CHMP 2B) in chromosome 3, discovered in a large Danish FTD family (Skibinski et al., 2005). Chromosome 9 linkage with familial ALS associated with FTD and a new mutation on the intraflagellar transport protein 74 gene (IFT14) have also been described (Momeini et al., 2006).

### **Epidemiology**

FTD is a not rare condition, as shown by an autopsy series where FLD and PiD were estimated to account for 20% of degenerative dementias (Brun et al., 1987). This proportion is higher when early onset dementias are considered.

Other autopsy studies have suggested a lower prevalence (Knopman et al., 2004), but the lower numbers may be related to underdiagnosis. A population-based study in the Netherlands estimated the prevalence of FTD to be 3.6 per 100,000 at age 50 to 59 years, 9.4 per 100,000 at age 60 to 69, and 3.8 per 100,000 at age 70 to 79. The median age at onset was 58 years (range 33-80) (Rosso et al., 2000). The typically younger age of onset, between the ages of 55 and 70, is an important diagnostic feature.

### **Diagnosis**

Neuroimaging, especially MRI, is essential, although it can be misread as negative in early stages. Commonly asymmetrical frontal and temporal atrophy is seen. Later in the illness the atrophy may become more diffuse. Metabolic imaging with FDG-PET may be more sensitive (Seeley et al., 2008), but SPECT scans are more widely available. CSF tau/ beta amyloid ratios and PIB compound imaging are being considered as biomarkers in differentiating FTD/Pick complex from AD (Bian et al., 2008; Rabinovici et al., 2007). Formal language testing and behavioral inventories are useful additions to a general neuropsychological assessment (Harciarek & Jodzio, 2005).

### **Prognosis and Treatment**

Frontotemporal dementias are variably progressive. The average duration of disease is 8-10 years from estimated onset to death, but the course can be as short as a few years to well over decades. The course is shorter in cases with motor neuron disease or early extrapyramidal involvement. There is evidence that cholinergic receptor binding is decreased in PiD in affected cortical regions (Yates et al., 1980). Serotonin and imipramine binding are decreased in the hypothalamus and frontal and temporal lobes in PiD (Sparks & Markesbery 1991). The decreased serotonin binding could correlate with the over-eating, sweet cravings, and weight gain observed in some patients with PiD/FTD/Pick complex. Other behavioral impairments, such as depression, irritability, and apathy with relative preservation of memory are also compatible with serotonergic dysfunction. SSRIs have been tried in an open label application in FTD patients, improving some of the obsessive symptoms (Swartz et al., 1997). Paroxetine on the other hand was ineffective in a small controlled trial (Deakin et al., 2004). Trazodone has been found to be efficacious in a placebo cross-over design to improve behavior in FTD (Lebert & Pasquier 1999).

Anecdotal reports of cholinesterase inhibitors causing worsening or improvement are not reliable. One case-controlled retrospective comparison showed a positive effect of rivastigmine in FTD (Moretti et al., 2004). Another placebo-controlled trial with galantamine (Kertesz et al., 2008) demonstrated some stabilizing effects on the course of PPA, but not bvFTD patients. Small doses of atypical neuroleptics are effective for controlling restlessness, roaming, and hyperactivity. Much of the current treatment is only symptomatic; thus far no drugs have shown disease-modifying properties. Lithium dephosphorylates tau *in vitro*, but in patients not only did it not



seem to be effective, but it produced enough side effects to require abandoning a trial (unpublished data from our clinic). Bromocriptine and intravenous administration of cerebrolysin were also ineffective in PPA in small unpublished trials. Systematic reviews of treatment have suggested a symptomatic effect for mainly serotonergic drugs (Huey, Putnam & Grafman 2006; Boxer & Boeve, 2007).

Caregivers of patients with FTD need counseling and ongoing support, especially as the disease progresses and results in social, family, and personality breakdown. Various support groups help to provide coping strategies and resources to families struggling with this disease.

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