DRUGS & AGING

abstract

Frontotemporal dementia (FTD or Pick's disease) is a relatively common but underdiagnosed form of presenile dementia. Estimated prevalence is 20% of dementias and 50% of dementia in patients under age 65. Common presentations are disinhibition with indifference; progressive aphasia; semantic dementia; unexplained falls, vertical gaze palsy, and dysarthria; and dementia with motor neuron disease. Neuroimaging is essential to exclude a slow tumour. Tau mutations are found in some families. Atypical neuroleptics and antidepressants can effectively treat some of the characteristics of FTD.

Key words: *frontotemporal dementia, Pick's disease, primary progressive aphasia, corticobasal degeneration, progressive supranuclear palsy*

Frontotemporal Dementia

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Introduction

Frontotemporal dementia (FTD) is synonymous with clinical Pick's disease (PiD). Many would prefer to continue using the latter term because of its obvious symmetry to Alzheimer's disease (AD), for the sake of lay audiences, and for historical accuracy. It would also simplify the current terminological confusion, since FTD is also used for the behavioural presentation of the disease. German neurologist Arnold Pick first described frontotemporal atrophy in a progressive aphasic patient with behavioural disturbances in 1892.[1] Subsequently, the term was restricted for only those with silver staining, round, intracellular inclusions (Pick bodies).[2] This resulted in the paradox of the disease being diagnosable only by pathologists! Since many typical clinical cases did not have Pick bodies, new labels such as frontal lobe dementia (FLD)[3] (later changed to FTD)[4] and primary progressive aphasia (PPA)[5] were created. Further development in pathological and clinical descriptions contributed to the proliferation of terms and a confusing alphabet soup of abbreviations (Table 1).

A collaborative group from Lund and Manchester, UK, who described dementia of the frontal lobe type, once again changed the terminology to frontotemporal lobar degeneration (FTLD) and summarized the consensus criteria for diagnosis.[6] FTLD, however, does not include the frequent subcortical involvement, parietal pathology, and extrapyramidal symptomatology. In 1994, we suggested the term Pick complex to incorporate the whole clinical syndrome and the pathological varieties underlying it.[7]

Frontotemporal Dementia—Behavioural Variant (FTD-bv)

The predominantly behavioural 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 a personality disorder. 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. Childish behaviour; rudeness; inappropriate sexual remarks; impatient, careless driving; excessive spending or hoarding of certain items; inappropriate joking; perseverative routines; compulsive roaming; insistence of certain foods; excessive food intake; neglect of personal hygiene; and disinterest in the immediate family are among the most characteristic features. The personality change often prompts the family to say that the patient is not the same person any more. Behavioural irregularities such as pilfering, shoplifting, swearing, undressing in public, and 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 tumours, lobectomies, and the common sequels of head injury ever since the classic description of the freak accident of Phineas Gage by a Vermont physician, John Harlow, in 1848. This conscientious, reliable, hard

Table 1: Glossary of Classifications of Frontotemporal Dementia, in Order of Approximate Frequency of Use

1. Frontotemporal dementia (FTD) Refers to both the behavioural variant, in this case FTD-bv, and the overall disease
2. Frontotemporal Degeneration (FTD) Used for all pathological variants Abbreviation is the same as clinical FTD
3. Frontotemporal Lobar Degeneration (FTLD) "Lobar" added to the overall pathological designation to reserve FTD for the behavioral presentation
4. Pick's Disease (PiD) The overall clinical syndrome, used less now, because of restricting it to item 2; preferred by many for simplicity and historical accuracy Histologically-defined entity, diagnosable only on postmortem with silver and tau-positive, round or oval inclusions in the cortex
5. Pick Complex (FTD/Pick) Includes all the clinical syndromes and underlying pathological variants FTD/Pick also used as a composite abbreviation combining items 1 and 5
6. Primary Progressive Aphasia (PPA) Slowly progressive aphasia before anything else develops Presenting syndrome is a major part of FTD/Pick Alternate term: Progressive Nonfluent Aphasia (PNFA)
7. Semantic Dementia (SD) Multimodal loss of meaning and difficulty with both comprehension and naming (especially nouns) Suggested alternative: semantic aphasia
8. Corticobasal Degeneration Syndrome (CBDS) Unilateral rigidity, immobility, apraxia, and the "alien hand," but many of these patients develop features of FTD and PPA Overlaps with PSP (10)
9. Corticobasal Degeneration (CBD) Basal ganglionic, and cortical silver and tau-positive neuronal inclusions, often look like Pick bodies, "Pick cells" are characteristic Also used as the clinical syndrome (as in 8)
10. Progressive Supranuclear Palsy (PSP) Defined by vertical gaze palsy, slowness, falling and dysarthria Overlap with CBDS (8) and CBD (9): symptoms, pathology, tau biochemistry, and genetics Probably part of Pick Complex; some prefer to keep it separate
11. FTD with Motor Neuron Disease (FTD/MND) Initially described as a clinical entity; identical to ALS-Dementia
12. FTD-Motor Neurone Disease Inclusion type (FTD-MND) Many cases of FTD with ubiquitin-positive, tau-negative inclusions, typical of MND but most have no clinical MND Alternate term: Motor Neuron Disease Inclusion Dementia (MNDID) Probably the most common pathological variety of the Pick complex
13. FTDP-17 Frontotemporal dementia and parkinsonism linked to chromosome 17 Tau mutations in less than half of studied families; first published family also had amyotrophy
14. Dementia Lacking Distinctive Histology (DLDH) Pathology without Pick bodies or typical CBD features Most turn out to have MND-type inclusions when looked for
15. Argyrophillic Grain Disease, ALS-Parkinsonism-Dementia complex, "Lytico-Bodig" (from Guam), Mesial Temporal Sclerosis, Neuronal Intermediate Neurofilament Disease (NIFID), Progressive Subcortical Gliosis, Tangle only Dementia Pathological entities of uncertain position that were considered by some to be part of the Pick complex at one time or another; clinical correlates need to be clarified

working foreman became irresponsible, ill mannered, indifferent, and incapable following an injury to his frontal lobes. Some of the more advanced behavioural syndromes of FTD resemble the so-called Kluver-Bucy syndrome, which is produced in monkeys by bilateral ablation of the temporal neocortex and the amygdala, and can occasionally be seen in humans after encephalitis. The behaviours consist of hyperorality from a sweet tooth to excessive eating, hypersexuality (mostly words and gestures), compulsive touching (also called utilization behaviour), and uninhibited exploration of the environment.[8]

The highly complex symptomatology requires a degree of pattern recognition. Early cases often puzzle first time observers. Regular neuropsychological testing reveals preserved episodic memory and visuospatial function, but a caregiver providing history or response to a questionnaire, such as the Frontal Behavioural Inventory,[9] is more useful. The inventory was designed as a series of structured questions scripted so that both the normal and abnormal negative aspects of the behaviours were included. Each item is scored on a scale of four, and the items are grouped as negative behaviours such as apathy, aspontaneity, 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 behaviours which may be associated with FTD. The second group of behaviours contained items of disinhibition such as perseveration, irritability, jocularity, irresponsibility, inappropriateness, impulsivity, restlessness, aggression, and hyperorality. A score of 30 is the cutoff for the behavioural variety of FTD.

Neuroimaging, especially MRI, is very helpful, although it can be misread as negative in early stages. It often shows both frontal and temporal atrophy, at times more on the right or nondominant side. Later in the illness, the atrophy may become more diffuse. Metabolic imaging is claimed to be more sensitive by some, and most centres use SPECT scans. At the very minimum, a CT scan must be done to exclude frontal tumours before the diagnosis is entertained. The definition of FTD consists of general clinical criteria, created at a 1998 consensus meeting (Table 1).[6] Unfortunately, these criteria do not include the movement disorders of CBD/PSP, incorporated at later meetings.[10,11]

Primary Progressive Aphasia (PPA)

First described by Arnold Pick, a more modern series of patients with progressive language deficit, before other cognitive domains were involved, was named primary progressive aphasia (PPA) by Mesulam.[5] The initial presentation of PPA is often with word-finding difficulty (anomia). In this respect, PPA patients are not much different from AD patients except they have relatively preserved memory and nonverbal cognition. Several varieties of PPA have been described: the more common nonfluent variety leading to mutism (the majority of published cases); the aphemic variety with verbal apraxia and stuttering initially; and semantic aphasia (dementia), where speech output remains preserved while the meaning of objects as tested by naming and comprehension appears to be lost.[12] PPA has been frequently described with progressive apraxia and extrapyramidal features (CBD). Most cases of FTD, if followed long enough, develop progressive language loss and mutism. PPA is most commonly associated with CBD and Pick body pathology.

Semantic Dementia

The patient asking the meaning of common nouns when they come up in conversation is characteristic in semantic dementia (e.g., "What is parade? Veal?").[12] Semantic dementia is frequently observed with the behavioural presentation of FTD, but relatively infrequent as a primary or isolated presentation. Episodic memory is preserved but memory for names or faces is lost early. This condition resembles the transcortical sensory aphasia seen with strokes, and is characterized by preserved repetition, phonology, and syntax, but prominent semantic paraphasias and poor comprehension. Although the patients are fluent, communication is significantly impaired.

Corticobasal Degeneration (CBD)/Progressive Supranuclear Palsy (PSP)

There have been several case descriptions of Pick's disease where the patients had prominent extrapyramidal features. Sometimes unilateral rigidity and Parkinsonism were the first symptoms to attract attention. Corticodentatonigral degeneration was described as a new disease, but the similarity of the pathology to PiD, as well the occurrence of dementia, aphasia, and personality change, was recognized by the authors.[13] The condition was relabelled corticobasal degeneration (CBD).[14] The syndromes of prominent apraxia, unilateral rigidity, and alien hand phenomenon are seen with non-CBD pathology, and typical CBD pathology often occurs with PPA or FTD without the

Table 2: Pathological Varieties of Frontotemporal Dementia

Clinical Presentation	Pick bodies	CBD/PSP	DLDH	FTD/MND
FTD (FLD)	++	+	+++	+++
FTD with MND	+	+	+	+++
PPA	++	+++	++	++
CBDS/PSP	++	+++	+	+

+++: most common; ++: common; +: less common or exceptional; FTD: frontotemporal dementia; FLD: frontal lobe dementia; MND: motor neuron disease; PPA: primary progressive aphasia; CBD: corticobasal degeneration; PSP: progressive supranuclear palsy; DLDH: dementia lacking distinctive histology

movement disorder.[15] We suggested that the clinical syndrome should be designated as corticobasal degeneration syndrome (CBDS) to distinguish it from CBD pathology.[15]

Progressive supranuclear palsy (PSP), also described as a new "Parkinson plus" syndrome,[16] is characteristically associated with dementia and speech disturbance. Although there are large advocacy groups for PSP as a distinct entity, the clinical, biochemical, pathological, and genetic overlap with CBD and CBDS is acknowledged by movement disorder clinicians and neuropathologists.[17] The evidence favours considering it along with CBD as the extrapyramidal component of the Pick complex.

Motor Neuron Disease and FTD

Recently, a great deal of interest has been shown in the association of dementia with motor neuron disease (MND).[18] It became 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 amyotrophic lateral sclerosis (ALS). The association of dementia with the MND-type inclusions was subsequently named motor neuron disease inclusion dementia (MNDID).[19] The MND-type inclusions have been found in FTD without clinical MND, even in the familial form. In fact, a majority of cases, which were previously described as having "dementia lacking distinctive histology,"[20] have these rather distinct inclusions.[21,22] In the familial cases, intranuclear inclusions of similar histochemistry have been recently discovered. There are a small but significant number of cases of FTD and PPA developing clinical MND (about 10%). Cognitive and behavioural impairment has been observed in ALS, and some estimate it to occur in as many as 50% of cases.

Neuropathology and Biochemistry

The underlying neuronal loss, gliosis, and superficial linear spongiosis in affected cortical areas are common to all histological subtypes. Ballooned neurons or Pick cells occur with variable frequency in all varieties. They appear swollen pink on H & E staining, lack Nissl substance (neuronal achromasia) of the cytoplasm, and express phosphorylated neurofilaments. The superficial layer spongiosis is seen in layers II and III of the cortex, in contrast to the spongiform change of Creutzfeldt-Jakob disease, which tends to be present throughout the cortex.

Various distinctive features, such as Pick bodies, astrocytic plaques in CBD, tufted astrocytes in PSP, and ubiquitin-positive, tau-negative inclusions in MND-type dementia, have been described and each given different disease names. However they, in turn, can occur with each of the other clinical varieties within the complex (Table 2). Cases lacking any of these distinctive features are often labelled "dementia lacking distinctive histology" (DLDH),[20] but many turn out to have the MND-type inclusions (MNDI). These inclusions are found in more than half of the FTD cases on autopsy and form the largest single pathological variety of Pick complex.[21] There is substantial overlap between all pathological varieties, although their distinctiveness is also argued.[17] Although the clinical varieties of the Pick complex do not predict the overall pathological spectrum, there is a prominence of tau-positive CBD or Pick body pathology in the extrapyramidal and aphasic presentation, and the tau-negative FTD-MND type with the behavioural presentation.

Abnormally phosphorylated and aggregated tau proteins are biochemical markers of various forms of degenerative dementia, including AD, PiD, CBD, PSP, the Parkinsonism-Dementia of Guam, and dementia pugilistica—collectively called tauopathies.

Genetics

A linkage to chromosome 17 q21-22 was discovered in a large family with variable behavioural symptomatology, aphasia, parkinsonism, and amyotrophy,[23] and the term "Frontotemporal Dementia with parkinsonism linked to chromosome 17" (FTDP-17) was accepted. Tau was suspected as the candidate gene for mutation, and a year later several tau mutations were discovered.[24] To date, about 30 Mandelian dominant tau mutations in more than 50 families have been identified.

Treatment

Cholinergic and serotonin binding are decreased in the hypothalamus, frontal lobes, and temporal lobes associated with PiD. The decreased serotonin binding may correlate with overeating, food preferences for bananas, sweet cravings, and weight gain in some patients with FTD/Pick complex. Other behavioral impairments, such as depression, irritability, and apathy with relative preservation of memory, are also compatible with serotoninergic dysfunction. SSRIs have been used in FTD patients, improving some of the obsessive symptoms. Trazodone has been found to be efficacious in a placebo crossover design to improve behavior in FTD.[25] Cholinesterase inhibitors have not been systematically tested, and anecdotal reports of worsening or improvement are not reliable. Small doses of atypical neuroleptics are effective to cope with restlessness, roaming, and asocial behaviour. Current treatment is symptomatic; so far, no drugs have shown disease-modifying properties. Caregivers with FTD need extra time for counselling, especially as the disease progresses and results in social, family, and personality breakdown.

Conclusion

Frontotemporal dementia or Pick Complex is an underdiagnosed but relatively frequent, presenile degenerative disease. The major components are behavioural, aphasic, and extrapyramidal. The extrapyramidal component is variously called corticobasal degeneration and progressive supranuclear palsy. Focal atrophy, neuronal loss, and gliosis are common to all; about half of recorded cases have tau positive neuronal and glial pathology, and the other half ubiquitin positive ALS-type inclusions. A relatively high familial incidence is at times associated with mutations on the tau gene.

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