PROGRESS IN CLINICAL NEUROSCIENCES: Frontotemporal Dementia-Pick's Disease

Andrew Kertesz

ABSTRACT: Frontotemporal dementia (clinical Pick's disease) is a relatively common, but underdiagnosed degenerative disease in the presenium. Estimated prevalence ranges from 6-12% of dementias. The behavioural, aphasic and extrapyramidal presentations are labeled FTD-behavioural variant, Primary Progressive Aphasia (PPA) and Corticobasal Degeneration/Progressive Supranuclear Palsy (CBD/PSP). The diagnostic features and course of each are described and their overlap in the evolution of the illness is emphasized. The neuropathology ranges from the most common tau negative ubiquitin positive amyotrophic lateral sclerosis (ALS) type inclusions to the tau positive classical Pick bodies and more or less distinct changes of PSP and CBD. The genetics of the relatively frequent tau mutations and the yet unsolved problem of tau negative families are discussed. The tau negative cases tend to be associated with the behavioural presentation and semantic dementia and the tau positive ones with PPA and the CBD/PSP syndrome. However the overlap is too great to split the disease. A glossary to navigate the proliferating terminology is included.

RÉSUMÉ: Démence fronto-temporale - maladie de Pick. La démence fronto-temporale (DFT - maladie clinique de Pick) est une maladie relativement fréquente mais sous-diagnostiquée chez les patients préséniles Sa prévalence serait de 6 à 12% chez les patients atteints de démence. Les manifestations comportementales, aphasiques et extrapyramidales sont considérées comme des variantes comportementales de la DFT, de l'aphasie progressive primaire (APP) et de la dégénérescence cortico-basale (DCB)/paralysie supranucléaire progressive (PSP). Nous décrivons les manifestations diagnostiques et l'évolution de chacune et nous soulignons leur chevauchement au cour de l'évolution de la maladie. La neuropathologie varie de la forme la plus fréquente qui est la présence d'inclusions de type DLA ubiquitine positives tau négatives, aux corps de Pick classiques tau positifs et aux changements plus ou moins distincts de la PSP et de la DCB. Nous discutons des aspects génétiques des mutations relativement fréquentes de la protéine tau et du problème non résolu des familles qui ne sont pas porteuses de mutations de cette protéine. Les cas tau négatifs sont en général associés à des manifestations comportementales et à une démence sémantique et les cas tau positifs à l'APP et au syndrome DCB/PSP. Cependant, le chevauchement est trop considérable pour en faire différentes entités. Nous ajoutons un glossaire afin de définir une terminologie en expansion.

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Frontotemporal dementia is a new name for clinical Pick's disease (PiD). Many would prefer to continue using the eponymic term because of its obvious symmetry to Alzheimer's disease (AD), for the sake of lay audiences and for historical accuracy. Arnold Pick described the clinical picture of frontotemporal atrophy a century ago. 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. Gans² suggested the eponymic term and considered a predilection for the phylogenetically younger frontal and temporal lobes in the etiology. The selective vulnerability of certain areas of the brain may indeed be responsible for the clinical and pathological diversity of the syndrome, but the reason for this, as well as the cause of the disease remains a mystery.

Subsequently, PiD was defined on the basis of histology, initially described by Alzheimer.² Onari and Spatz³ re-examined a series of cases of Pick and others, emphasizing this histological picture, particularly the round inclusions or Pick bodies, associated with focal atrophy. Subsequent reports of PiD, based on postmortem examination, often had the clinical features

From the Department of Clinical Neurological Sciences, St. Joseph's Hospital, University of Western Ontario, London, Ontario, Canada.

RECEIVED AUGUST 9, 2005. ACCEPTED IN FINAL FORM NOVEMBER 18, 2005. Reprint requests to: Dr. Andrew Kertesz, Department of Clinical Neurological Sciences, St. Joseph's Hospital, University of Western Ontario, London, Ontario, N6A 4V2, Canada. incompletely described because of the retrospective nature of these studies. This gave rise to the notion that PiD is difficult to diagnose in vivo. It also became apparent that cases of clinical PiD with frontal lobe and temporal lobe symptomatology may not show the typical histological picture of Pick bodies. A dichotomy of nosology arose because some people use the term PiD on the basis of histological criteria, while others describe the clinical picture of frontotemporal atrophies as Pick did originally. After reviewing a large series, Constantinidis et al.⁴ classified PiD as variety A) with Pick bodies, B) only with swollen neurons, and C) only gliosis. They felt "in spite of the dissimilarities between these forms, considering the absence of sufficient knowledge about pathogenesis, it seems prudent at present to maintain the uniqueness of Pick's entity."

Frontotemporal atrophy was demonstrated with increasing frequency in vivo, first with CT scans in the 1970s and MRI scan and SPECT more recently. The in vivo diagnosis of PiD continued to be made sporadically on the basis of dramatic behavioral symptomatology supported by neuroimaging. However, instead of shifting the diagnosis of PiD back to the clinic, several studies applied new labels such as frontal lobe degeneration (FLD) or dementia of the frontal lobe type^{6,7} and subsequently frontotemporal dementia (FTD)⁸ and frontotemporal lobar degeneration (FTLD). 9 These terms were initially applied mainly for the behavioral presentation, while reserving the diagnosis of PiD to the postmortem finding of Pick bodies This gave rise to the paradox that Pick's disease, a former clinical entity, could only be diagnosed by pathologists! Further development in pathological descriptions contributed to the proliferation of a veritable alphabet soup of terms (see glossary).)

In order to alleviate the nosological dichotomy and use a historically correct term, yet retain the well-established eponym, we suggested the term "Pick complex" (PC) to encompass all the related entities both clinically and pathologically. In a recent consensus conference the use of FTD for the overall syndrome was found to be most common, although it has continued to be used for the behavioural presentation also. The major presentations of FTD are discussed separately, but it should be remembered that they are overlapping manifestations of the same disease. The myth that this is a rare condition was challenged by the first autopsy series where FLD and PiD was estimated to be 12% of degenerative dementias. 5

Frontotemporal Dementia- Behavioral 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 an obsessive-compulsive or a sociopathic 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. When the striking disinhibition and asocial behaviour appear the diagnosis is unmistakable, once head injury, stroke and tumor are eliminated. Most of these are evident on history, 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 of certain foods, excessive food intake, neglect of personal hygiene, disinterest in the immediate family, or others are the most characteristic features. 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 the common sequels of head injury ever since the classic description of the freak accident of Phineas Gage, a conscientious, reliable hard working foreman, who became irresponsible, ill mannered, indifferent and incompetent, following a tamping iron blown through his frontal lobes. Harlow, his physician commented on the change of personality: Gage was not Gage any more. Some of the more advanced behavioural syndromes of FTD resemble the so-called Kluver-Bucy syndrome, ¹⁴ which is produced in monkeys by bilateral ablation of the temporal lobes and can be seen in humans after encephalitis, consisting of hyperorality (first a sweet tooth, then excessive eating of anything), hypersexuality (mostly words and gestures), compulsive touching (also called utilization behavour), and disinhibited exploration of the environment.

Neuropsychological deficits have been variable because of the types and methods of patient selection at different stages of illness and the tests used. 15-17 The Mini-Mental Status Examination may be normal in early cases. Frontal lobe functions are impaired. However, some patients with behavioural presentation perform well on "frontal" tests especially if they are seen early. Although FTD can present as a "dysexecutive syndrome", frontal lobe or executive deficits are often involved in AD as well. Recognition memory appears better than recall and the patient tends to benefit from multiple-choice alternatives, but most of the neuropsychological screening batteries in use only test recall. Those FTD patients who could carry out detailed memory tasks performed better on the WMS relative to AD patients, although preservation of memory is not universal by any means. There is often a memory complaint in FTD, but the reason for impaired memory performance could be related to inattention, lack of motivation, and/or language impairment. Orientation and episodic memory is relatively preserved. Conversely, there may be impaired test scores on immediate and delayed recall of a story, yet the patient can recall personally relevant events, which is quite out of keeping with impaired test scores. This seeming paradox contributes to the degree of variability in reported memory impairment in FTD cases.

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 requiring executive function, such as trail-making, are impaired at an early stage, but block design and Raven's Coloured Progressive Matrices may be preserved. At times, impulsivity, disinhibition, perseveration, echopraxia and utilization behaviour are observed during neuropsychological testing. In later stages, the patient may be too restless or language impaired to test.

A caregiver providing history and responses to a questionnaire, such as the "Frontal Behavioral Inventory", 18 to

be used at the initial interview or for retrospective diagnosis, turns out to be the most useful diagnostic tool. The inventory was designed as a series of structured questions scripted so both the normal and abnormal aspects of the behaviours were included. Each item was scored on a scale of 4: 0 = none, 1 = mild oroccasional, 2 = moderate, 3 = severe or most of the time. The items were 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 behaviors contained items of disinhibition such as perseveration, irritability, jocularity, irresponsibility, inappropriateness, impulsivity, restlessness, aggression, hyperorality. A score of 30 is cutoff for FTD-bv. We demonstrated in a study with the behavioural inventory that using cognitive tests only 75% of FTD and AD patients can be distinguished; by adding FBI to the discriminant function, 100% discrimination was achieved. 19

Neuroimaging, especially MRI, is very helpful, although it can be misread as negative in early stages. It often shows asymmetric frontal and temporal atrophy. Later in the illness the atrophy may become more diffuse. Metabolic imaging is claimed to be more sensitive by some. The SPECT scans are more widely available. At least a CT must be done to exclude frontal tumors, before the diagnosis is entertained. Behavioural manifestations, are more likely to be presented to a psychiatrist than to a neurologist. Neurologists, on the other hand, may see the primarily aphasic or movement disorder more often. The complex symptomatology requires a degree of pattern recognition. Early cases often remain puzzling for first time observers.

In summary, the diagnosis of FTD-bv depends on a good history from a caregiver. The emergence of food fads, gluttony, rudeness, poor judgment, indifference, hoarding, and childish joking in a presenile individual with relatively retained memory and spatial cognition should ring an alarm bell. A frontal behavioural inventory and confirmation with neuroimaging are desirable. AD patients are older, have major memory and visuospatial deficit, and diffuse atrophy. Exclusion of brain tumor, vascular dementia and manic depressive illness is essential.

Primary Progressive Aphasia

Although described by Pick almost a century before, as part of circumscribed frontotemporal atrophy, relatively pure progressive language deficit was named primary progressive aphasia (PPA) by Mesulam.^{20,21} Detailed modern case reports of Pick's disease with progressive aphasia appeared at the same time.^{22,23} The term PPA has been widely used, although similar patients were reported under variations of this terminology, such as progressive aphasia without dementia,²⁴ progressive nonfluent aphasia,²⁵ and pure progressive aphemia.²⁶ The condition was considered a separate entity for a while, but the evidence was presented to consider it part of Pick complex/FTD.¹⁰

The initial presentation of PPA is often with word finding difficulty, or anomia. In this respect, PPA patients are not much different from Alzheimer patients, except they have relatively preserved memory and non-verbal cognition. By the time they

show aphasic difficulty, AD patients already have significant memory loss, disorientation, constructional, visuospatial, and other cognitive impairment. The relatively isolated language disturbance in the first two years of the illness was suggested by Mesulam as the operational definition of PPA. However, some cases have behavioural or extra-pyramidal features which appear before the two year deadline.

The more typical clinical picture progresses from anomia to a non-fluent type of aphasia with increasing word finding difficulty. Logopenia is defined as prominent word finding difficulty, but the phrase length is still longer than four words and syntax is preserved.²⁷ Decreasing speech output involves spontaneous speech first and repetition is affected to a lesser extent initially.²⁸ Sometimes the aphasic disturbance resembles Broca's aphasia with grammatical errors and phonemic paraphasias. The relative preservation of comprehension is typical, and nonverbal intelligence and episodic memory are demonstrably maintained.^{29,30} Broca's aphasia with agrammatism is more characteristic of stroke patients but it may be seen in PPA as a transient stage, usually progressing with increasing word finding difficulty to mutism. The course is variable, may be quite prolonged, but sometimes patients who develop pathology in the basal ganglia or motor neuron disease, progress quickly and develop difficulty with swallowing and choking; the duration may be as short as two years from onset to death.10

Some patients present with stuttering or slow, segmented speech and verbal apraxia, which includes articulatory difficulty and phonological paraphasias. Cortical dysarthria, anarthria, aphemia, or pure motor aphasia are alternative terms to describe the phenomena. The articulatory impairment is characterized by particular difficulty with initial consonants, such as omission, repetition, and substitution. Although this is often called verbal apraxia, it may occur with or without buccofacial or limb apraxia. These patients are less likely to be mistaken for AD. A progressive limb apraxia can be a prominent feature, Indicating a clinical overlap between PPA and the apraxic-extrapyramidal syndrome of Corticobasal Degeneration (CBD).

Some patients, well after many years of illness, continue to function normally at home even though they are completely mute. Mutism has been considered characteristic of PiD, and it tends to be the end-stage of all forms of frontotemporal dementia (FTD), even those which start with behavioral abnormalities rather than language disturbance. End-stage mutism also occurs in AD, but usually in a patient who already has a 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, fluent form of PPA that is different from the more common non-fluent variety was described as 'semantic dementia' by Snowden et al.³³ These patients progressively lost the meaning of words but retained fluency and were able to carry out a conversation. Subsequent descriptions of this entity adopted this term,³⁴ and more recently it has been used extensively. Semantic aphasia was a term used by Henry Head³⁵ for a two-way disturbance of comprehension and naming. The picture is similar to 'transcortical sensory aphasia' in which

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articulation, phonology and syntax remain intact but the patient does not comprehend well and has word finding difficulty. Initially they 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 with a rather selective loss of semantic memory. Some very interesting studies showed these patients retain information that has immediate relevance to their environment or to their person, yet lose the meaning of other common things. The behaviour can be so dissociative that some of these patients are considered hysterical, or schizophrenic. Semantic dementia is often associated with FTD-bv and patients presenting with the behavioural symptoms often have elements of semantic dementia.

Standardized language testing is useful to diagnose and follow the course of illness of both PPA and semantic dementia. Particularly important is to examine spontaneous speech for fluency and content, to document comprehension and naming, preferably with low and high frequency items, and repetition. Reading and writing are also important, particularly a list of irregular words to detect transcortical alexia (reading without meaning). Additional psycholinguistic testing is of considerable interest in exploring the processing deficit, particularly semantic dementia. 34,36

Corticobasal Degeneration/Progressive Supranuclear Palsy

There have been several case descriptions of PiD where the patients had prominent extra-pyramidal features.³⁷ Sometimes unilateral rigidity and Parkinsonism were the first symptoms to attract attention. It was recognized that subcortical changes occur in PiD, even without extrapyramidal symptomatology.^{38,39}

When Rebeiz et al⁴⁰ 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 or corticobasal ganglionic degeneration. 41,42 Including the original description, which had speech and behavioural change, most of the literature concerning this condition acknowledge the clinical and pathological overlap between CBD and PiD.43,44 CBD is suffering from similar dichotomy as PiD in that the pathological and clinical descriptions do not fully match. There are some case reports describing patients presented clinically as CBD, as defined by unilateral rigidity, apraxia and alien hand syndrome, but who have the pathological findings of PiD with Pick bodies. 45 Other cases pathologically typical of CBD have FTD or PPA without the extrapyramidal features. 46 We suggested that 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.⁴⁷

Neuropathologically selected CBD series showed a high incidence of cognitive deficit, frontal lobe symptomatology, and progressive aphasia. In one series from a brain bank the most common presentation was "dementia". Our experience with CBDS showed significant overlap between CBDS and the syndromes of FTD/Pick complex. All of our 35 patients with clinical CBDS either had a language disorder or a behavioural

and personality change characteristic of FTD. At times the movement disorder and the progressive aphasia or behavioural disorder developed simultaneously, but in the majority of the cases the cognitive disorder came first (n = 20). Similarly, in all the primary movement presentations (n = 15), aphasic or behavioural change has developed sooner or later, indicating that CBDS should be considered part of the Pick complex. In 11 of our cases with autopsy, out of a clinical series of 35, six had CBD pathology (one considered having features of PSP), three cases had PiD, one had motor neuron disease (MND)-type inclusions, and one dementia lacking distinctive histology (DLDH).⁴⁴

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,50 but the overlap with CBDS has been increasingly recognized lately.⁴³ In the original description eight of nine cases had significant dementia or personality change, often as a presenting feature, yet the disease remained in the realm of movement disorder. Later it became the prototype of the description of subcortical dementia.51 Some studies comparing the neuropsychological features of PSP and CBD found no significant difference between them and they pointed out the impairment of the subcortical-frontal connections.⁵¹ Many CBD patients also have vertical gaze palsy; some have falls, and symmetrical extrapyramidal syndrome.⁵² The pathological features are also considered to be overlapping to a great extent.⁴³ Biochemical and genetic evidence also support the relationship. 53,54 They are both considered to be predominantly 4 repeat tauopathies. They have common tau haplotypes. There is continuing controversy to what extent PSP and CBD can be differentiated, although pathological criteria for each have been validated recently.⁵⁵ The evidence suggests that CBD/PSP is also part of the Pick complex pathologically and clinically, although the concept remains controversial to some extent.

Motor Neuron Disease and Frontotemporal Dementia

Recently a great deal of interest has been shown in the association of dementia with MND. 56,57 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). 58 Subsequently these were named motor neuron disease inclusion dementia (MNDID). 59 Many had FTD-like features. In group studies the description of the dementia was more cursory. Cognitive and behavioural impairment has been observed in ALS and some estimate it to be as high as 50%. 60,61 However not all of them have FTD, perhaps only half of those. There are also a significant number of cases of FTD and PPA developing MND. 57,62

In more than half of the cases of FTD ubiquitin positive tau negative inclusions are found without clinical MND and similar tau negative pathology is common in the familial form.⁶³ In the familial cases intranuclear inclusions of similar histochemistry have been discovered recently.⁶⁴ The majority of cases, which were previously described as having "dementia lacking distinctive histology" have these rather distinct inclusions if ubiquitin stains are used, also called FTD with MND type inclusions or FTD-MND.⁶⁵⁻⁶⁷

Neuropathology

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, lack Nissl substance (neuronal achromasia) of the cytoplasm, and they 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 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, but they, in turn, can occur with each of the other clinical varieties. Cases lacking any of these distinctive features are often labelled "dementia lacking distinctive histology," (DLDH)⁶⁸ but many turn out to have the MND-type inclusions (often abbreviated FTD-MND type or MNDI) if they are stained with ubiquitin. These inclusions are found in more than half of the FTD cases on autopsy and form the largest single pathological variety of Pick complex. 65-67 They appear similar in location and morphology to Pick bodies, but differ in their histochemical characteristics.

There is substantial overlap between all pathological varieties, although their distinctiveness is also argued. The clinical varieties of Pick complex do not predict the specific pathology, only the overall pathological spectrum, but there is a prominence of tau positive CBD or Pick body pathology in the extrapyramidal and aphasic presentation, and the tau negative FTD-MND or DLDH type with the behavioural presentation and semantic dementia. Progressive subcortical gliosis clinically and pathologically similar to other varieties and remains so far only a doubtful pathological distinction. Argyrophyllic Grain Disease, Tangle Only Dementia, Mesial Temporal Sclerosis and Neuronal Intermediate Neurofilament Inclusion Disease have been classified at one time or another as possible pathological variants of the complex.

Biochemistry

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, dementia pugilistica, etc., collectively called tauopathies. However, tau mutations have been discovered only in frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17). Neurofibrillary tangles (NFT) of AD contain all six human tau isoforms. Abnormally phosphorylated tau forms three bands on Western blot studies with a molecular weight of 55, 64, and 69 kDa in AD. PiD has a 64-kDa and 55-kDa, and CBD and PSP 69 and 64 kDa doublets. The amounts of abnormal tau can be low in FTD and sometimes it is absent. At times FTD has the same tau triplet as in AD. Sometimes different band compositions are obtained from different parts of the brain.

Normal tau proteins are contributing to axonal transport by binding to microtubular protein.^{71,73} Six tau isoforms are created by the differential splicing of Exon 10 making 3 or 4 repeat of the microtubular binding domain of tau. Three repeat (3R) tau predominates in PiD and 4R tau is more common in CBD and PSP. Lately 4R tau is shown with equal frequency to 3R tau in

PiD in some cases and the biochemical differences may not be as sharp as it was previously thought.⁷² Tau negative "hereditary dysphasic disinhibition dementia" and some sporadic cases of DLDH with prominent language and behavioral deficit have been more recently attributed to the loss of normal tau in the brain with the same effect as the "tauopathies" with tau positive pathology.⁷⁴

MND Inclusions are ubiquinated and tau and synuclein negative, therefore considered ubiquinoathies. It appears that at least, if not more, 50% of FTD belong to this category biochemically and pahologically.⁶⁵⁻⁶⁷ Valosin related protein involved in ubiquitin binding and found in intranuclear inclusions, co-localizing with ubiquitin, may play a role in the pathogenesis⁷⁵ (see below).

Genetics

Wilhelmsen et al. ⁷⁶ discovered linkage to chromosome 17 q21-22 in a large family with variable symptomatology of FTD, aphasia, Parkinsonism, and amyotrophy. ⁷⁷ 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. ⁷⁸ The microtubular associated protein tau was suspected as the candidate gene for mutation and later several tau mutations were discovered. ^{73,79,80}

To date, more than 30 tau mutations in more than 50 Mendelian dominant families have been identified. 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. Often the same mutation such as the common P301L may produce pathology with Pick bodies, CBD, or DLDH.81 The missense mutations disrupt the interaction between tau and microtubules, and unbound tau becomes abnormally phosphorylated and polymerized into filaments and inclusions. Mutations in Exons 9, 12, and 13 result in either accumulation of all six isoforms of tau forming tangles or in a predominance of 3 repeat tau and Pick body dementia. Although different tau mutations differentially alter biochemical properties of tau isoforms, these mutations do not predict the clinical presentations but they do predict the overall picture resembling sporadic Pick complex.

Tau polymorphisms, from the two main haplotypes of tau, were also studied. H1 haplotype is overrepresented in both PSP and CBD⁵³ and in FTD.⁸² The search for another genetic locus for the large number of tau negative families is under way. So far linkage to chromosome 3⁸³ and 9⁸⁴ have been demonstrated but no mutations found. The chromosome 9 linkage was shown with familial ALS associated with FTD. Mutation in the Valosin containing protein, on chromosome 9p13-12, which is involved in ubiquitin binding is associated with Inclusion body myopathy, Paget's disease and FTD.⁷⁵

Treatment

There is evidence that cholinergic receptor binding is decreased in PiD in affected cortical regions. ^{85,86} Serotonin and Imipramine binding were decreased in the hypothalamus, frontal and temporal lobes in PiD. ⁸⁷ The decreased serotonin binding could correlate with over-eating, food preferences for bananas for instance, 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 serotoninergic dysfunction. Selective serotonin reuptake inhibitors (SSRIs) have been tried in an open label application in FTD patients improving some of the obsessive symptoms. Trazodone has been found to be efficacious in a placebo cross over design to improve behavior in FTD.

Anecdotal reports of Cholinesterase inhibitors causing worsening or improvement are not reliable. One case controlled retrospective comparison showed positive effect of Rivastigmine⁹⁰ and in another trial with Galantamine⁹¹ some stabilizing effects on the course of PPA, but not FTD-by patients. Antioxidant Iodoxan have been tried with some benefit in only a few cases. 92 Small doses of atypical neuroleptics are effective to cope with the restlessness, roaming, and hyperactive behavior. Much of the current treatment is only symptomatic. So far, no drugs have shown disease modifying properties. Lithium dephosphorylates tau in vitro, but in patients not only did it not seem effective, but produced enough side effects to abandon a trial (unpublished data from our clinic). Bromocriptin and intravenous administration of Cerebrolysin were also ineffective in PPA in small unpublished trials. We also tried Ritalin in a restless patient, based on the analogy of ADHD treatment, but no effect was observed.

Caregivers of FTD patients need counseling, and ongoing support, especially as the disease progresses and results in social, family, and personality breakdown. Various support groups have been helpful to provide coping strategies and resources to families struggling with this disease. There are actively maintained websites by the US FTD Association: www.ftd-picks.org and in the UK: www.pdsg.org.uk.

CONCLUSIONS

Frontotemporal dementia or Pick's disease (Pick complex) is a relatively common, but still under diagnosed presentile degenerative dementia. Estimated prevalence ranges from 6% to 12 of dementias with a ratio of 1:5 to AD and 1:1 in early onset dementia (under age 65). The lack of reliable prevalence data stems from the difficulty in identification of cases, and a negative bias in autopsy series from brain banks affiliated with Alzheimer centers. The high estimates come from centers interested in the disease and may represent a positive bias. The familial incidence of FTD is high, approximately 30-40% of cases, but tau mutation is found only in about 10% of the families tested in some centers, and so far not in any sporadic cases. The detection of increased tau in the CSF is not specific and is unreliable, and so far the diagnosis depends on good clinical acumen and neuroimaging.

Frontotemporal dementia should be considered with the following scenarios: 1. disinhibition with indifference appearing in middle age (excluding advanced Alzheimer patients), 2. dysexecutive syndrome, unexplained failure with complex tasks, "burnout" without depression, 3. progressive unexplained aphasia, 4. patients with progressive comprehension deficit, who ask, "What is steak?," "shoepolish?", etc., 5. progressive apraxia and a unilateral, rigid, levitating or "alien" hand, 6. patients who fall and have vertical gaze palsy, 7. dementia with motor neuron disease.

About half of the cases coming to autopsy have a tau positive pathology, which could be CBD, PSP or Pick bodies. Among these the clinical features of CBDS is often associated with PPA and the tau negative cases, many with ALS inclusions, are commonly associated with the behavioural syndrome and semantic dementia. However there are many exceptions to this dichotomy and the evidence favours the unity of the complex. In other words FTD/Pick complex is one, not two, syndromes.

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GLOSSARY

1. Frontotemporal dementia(FTD)

Used for both the

- 1. Behavioral presentation, and
- 2. The overall disease.

2. Frontotemporal Degeneration (FTD)

- 1. Used for all pathological variants.
- 2. Also used (less correctly) as the clinical disease. The abbreviation is the same as clinical FTD.

3. Frontotemporal Lobar Degeneration (FTLD)

- 1. Lobar was added for the overall pathological designation to reserve FTD for the behavioral presentation.
- 2. Also used for the overall clinical disease.

4. Pick's Disease (PiD)

- 1. The overall clinical syndrome, used less now, because of restricting it to 2.
- 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 is also used throughout this article combining 1 and 5 as a composite abbreviation.

6. Primary progressive aphasia (PPA)

Slowly progressive aphasia before anything else develops. This presenting syndrome is also part of FTD/Pick. It also has a variety of pathologies just like FTD.

7. Semantic dementia (SD)

A multimodality loss of meaning, difficulty with both comprehension and naming, especially nouns. The loss of meaning extends to visually presented stimuli.

8. Corticobasal Degeneration Syndrome (CBDS)

Unilateral rigidity, immobility, apraxia, and the "alien hand", but many of these patients develop features of FTD and PPA. It 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.
- 2. Also used as the clinical syndrome (like in 8).

10.Progressive Supranuclear Palsy (PSP)

Defined by vertical gaze palsy, slowness, falling and dysarthria. The symptoms, pathology, tau biochemistry, and genetics overlap with CBDs(8) and CBD(9). Probably part of Pick Complex. Some prefer to keep it separate.

11. FTD with Motor Neuron Disease (FTD/MND)

This was 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. Also called 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. Less than half of these families have tau mutations. The first published family also had amyotrophy (MND).

14. Dementia Lacking Distinctive Histology (DLDH)

Pathology without Pick bodies or typical CBD features. Most of these turn out to have MND type inclusions when looked for.

15. Argyrophillic Grain Disease, ALS-Parkinsonism-Dementia complex, ("Lytico-Bodig") of Guam, Mesial Temporal Sclerosis, Neuronal Intermediate Neurofilament Disease (NIFID), Progressive Subcortical Gliosis, Tangle only Dementia