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Frontotemporal Dementia: An Updated Discussion and Local Case Vignettes

Connie T Y Yan

Department of Psychiatry, Prince of Wales and Shatin Hospital

Joshua M Y Tsoh

Department of Psychiatry, The Chinese University of Hong Kong

Abstract

This article reviews the updated scientific findings from the medical literature and from a recent International Conference on Frontotemporal lobar degeneration (FTLD) and clinical syndromes of frontotemporal dementia (FTD) in September 2016, regarding the epidemiology, diagnosis and treatment aspects of the condition. In addition, the authors shared potentially useful and practical approaches towards non-pharmacological treatment in FTD with two local case vignettes with the wish to attract more fruitful discussions on strategies to handle the clinical symptoms and enhance the quality of life of persons with FTD when no curative treatments are available. These are important given the fact that a rapidly rising number of persons are affected in Hong Kong and globally alike with population ageing (as most of the cases' clinical syndrome took onset in their sixth decades of life).

Keywords: Dementia, Ageing, Epidemiology, Treatment, Diagnosis, Frontotemporal Dementia (FTD)

Introduction

Frontotemporal dementia (FTD) is increasingly gaining recognition as a clinically heterogeneous syndrome of progressive decline in behavioural, executive, language or even motor functions associated with frontal and anterior temporal lobe degeneration (Rabinovici & Miller, 2010). For those delving into more recent literature on the subject, they often encounter the term "Frontotemporal lobar degeneration (FTLD)" which is defined as a pathologic endophenotype with the aforementioned characteristic atrophy leading to three clinical FTD syndromes with partially overlapping microscopic pathology (Karageorgiou & Miller, 2014). These are the behavioural variant frontotemporal dementia (bvFTD) and two types of the primary progressive aphasias (PPA) – namely the nonfluent-agrammatic (nfvPPA) and the semantic (svPPA) variants.

Correspondence concerning this article should be addressed to Dr. Joshua Tsoh, Consultant in Psychiatry, New Territories East Cluster (NTEC) C/o Department of Psychiatry, Shatin Hospital, N.T., Hong Kong
Email: tsohmy@ha.org.hk

Each of these has a unique neuroimaging pattern yet there are common molecular bases involving the accumulation of tau, transactive response DNA binding protein (TDP-43) and other pathological proteins (Rademakers, Neumann & Mackenzie, 2012).

Epidemiology and Prevalence

Epidemiologically, FTLD is more common than expected by most clinical practitioners. In the United States, the incidence of FTLD is estimated to be 3-4 per 100,000 person-years, with approximately 20,000 to 30,000 cases at a given moment (Knopman & Roberts, 2011). It is also the third common cause of degenerative disorder with dementia after Alzheimer's Disease and Lewy Body Dementia, accounting for 5 to 15% of all pathologically confirmed cases (Rademakers et al., 2012; Snowden, Neary and Mann, 2002). The picture is similar in all parts of the world with FTLD being the second most common cause of presenile neurodegenerative dementia in clients younger than 65 (Vieira et al., 2013), though some subtypes manifest older onset and slower disease progression (Hodges, Davies, Xuereb, Kril & Halliday, 2003; Hokoishi et al., 2001; Panegyres, Davies, & Connor, 2000; Panegyres & Frencham, 2007). The age of onset is typically in the sixth decade though some may present later (Hodges et al., 2003; Johnson et al., 2005; Ratnavalli, Brayne, Dawson, & Hodges, 2002).

What about our locality? In a previous discussion by the authors (Tsoh & Yan, 2014), it was stated that an updated prevalence of FTLD is yet to be formally reported in Hong Kong. Currently, however, there is an ongoing study by a local neurology team (The Chinse University of Hong Kong, 2016) and more accurate figures are expected to be published in the coming year or two. From the preliminary data of their registry – now sixty and still growing, Au et al. (2016) reported FTD being the second most common early-onset dementia, echoing the worldwide picture. Although an earlier study profiling attendees of a memory clinic only diagnosed 1.8% of their 385 demented subjects with FTD (Sheng, Law, & Yeung, 2009), it was notable that one-tenth (10.9%) of the group was labelled with "other irreversible" or "undetermined" dementia. Since FTD has been reported to be as common in Asians as in Caucasians (Hou, Yaffe, Perez-Stable, & Miller, 2006), possible reasons for this apparent discrepancy in prevalence and in diagnostic rate include the late presentation of Asian patients (Chao et al., 2013; Ghosh, Dutt, Ghosh, Bhargava, & Rao, 2013) as well as the absence of diagnostic criteria for early detention and identification of FTD in Asians (Ghosh et al., 2013; Sheng et al., 2009).

FTD Syndromes and Diagnosis

What one might proceed to ask is, if FTD is so common, why then are we not seeing more FTD cases? The answer is heterogeneity. Despite the creation of revised consensus criteria for both bvFTD and PPA (Gorno-Tempini et al., 2011; Rascovsky et al., 2011) that attempt to integrate the developments in neuroimaging, histopathology and genetics with clinical features and cognitive profiles to improve early diagnostic accuracy, this is no easy task – as even family members with a single genetic mutation can exhibit heterogeneous phenotypes. Karageorgiou and Miller (2014) have neatly summarized the pathological convergence associated with specific clinical syndromes and the syndromic divergence within pathologies in FTLD (Figure 1).

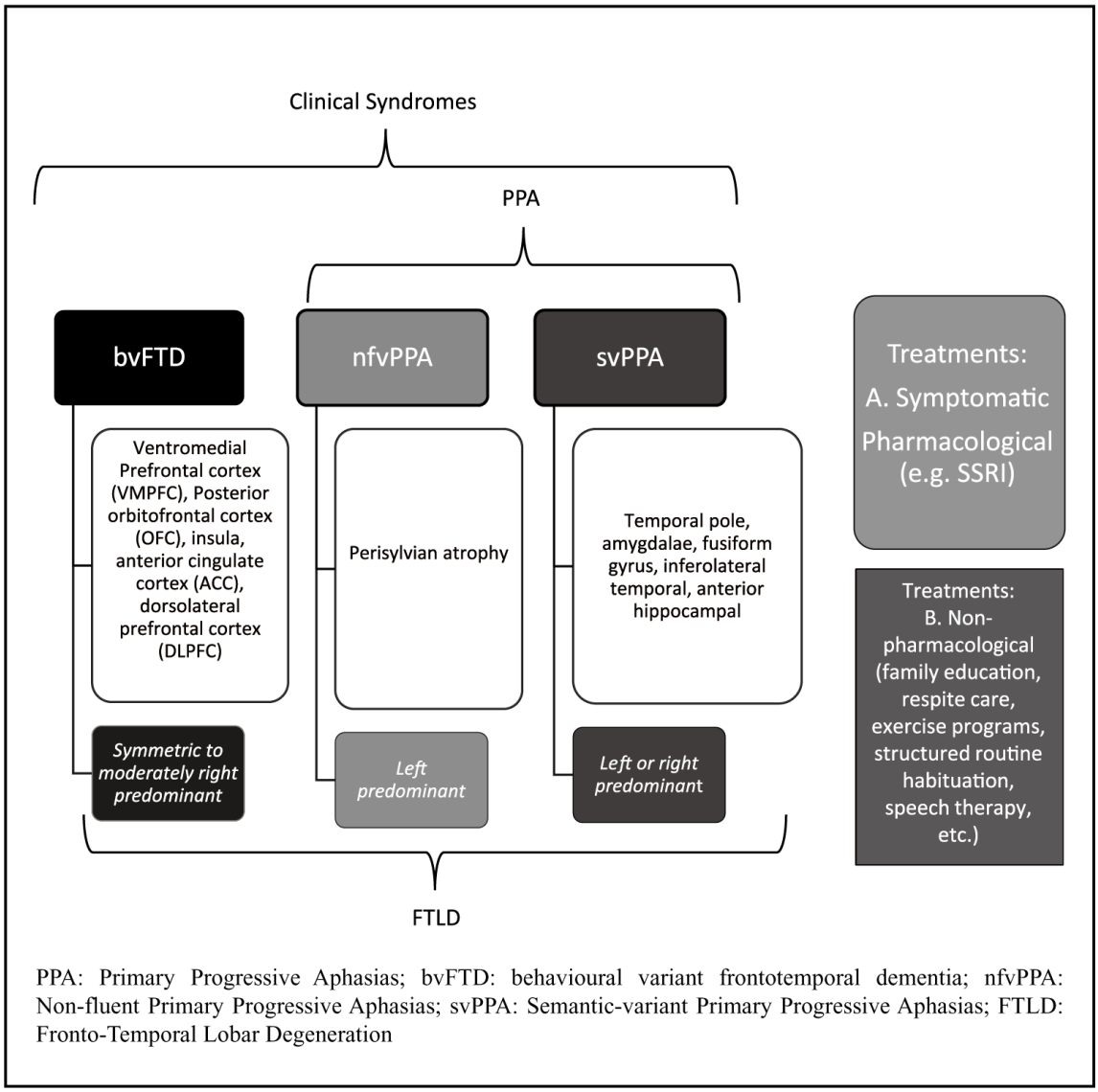

Figure 1: FTLD Phenotypes, brain atrophy patterns and treatments
(modified from Karageorgiou & Miller, 2014)

The previous understanding of FTD remains largely phenotypical and we are more familiar with the concepts raised by Neary et al. (1998) that the three FTD clinical syndromes – behavioural variant frontotemporal dementia (bvFTD), semantic dementia (SD) and progressive non-fluent aphasia (PNFA) – may overlap in presentation, especially with spreading degeneration later in the disease course. Hence the principle in FTD diagnosis and management is to first to exclude treatable and reversible causes that mimic FTLD, such as metabolic disturbances, nutritional deficiencies, CNS infections, substance abuse, vascular disease, heavy metal toxicity, primary neoplastic and paraneoplastic conditions (Rabinovici & Miller, 2010).

The key relevance of FTD to psychiatrists lies in the point that a common misdiagnosis

for FTD is a functional psychiatric disorder, though a small subset of bvFTD patients do have a comorbid psychiatric, usually affective, disorder (Davies et al., 2006; Kipps, Nestor, Dawson, Mitchell, & Hodges, 2008). As described by Wittenberg et al. (2008), bvFTD patients show marked personality changes, behavioural disturbances and impaired insight while their cognitive decline is less striking and mainly consists of frontal and executive deficits. There is, then, little wonder that FTD is often misdiagnosed as a psychiatric illness (Tsoh & Yan, 2014).

A newer approach suggested by Karageorgiou and Miller (2014) regards FTLD as an outcome of the selective vulnerability of specific neuroanatomical networks to neurodegeneration (Seeley, Crawford, Zhou, Miller & Greicius, 2009). Degeneration for all three FTD clinical syndromes – bvFTD, nfvPPA and svPPA – starts within a hub and spreads across the respective network like prion diseases, resulting in the unique clinical characteristics seen at each stage of the disease (Kfoury, Holmes, Jiang, Holtzman & Diamond, 2012; Guo et al., 2013). In that case, it becomes crucial to elucidate the temporal course of symptoms and cognitive decline and then to deduce their neuroanatomical representation and brain atrophy progression. The aim of diagnosis is to first recognize the phenotypic syndrome, and then to work out the most likely proteinopathy and possible genetic mutation (Rosen, Gorno-Tempini, Goldman & Miller, 2002). Along this line, researchers hope to improve diagnostic and prognostic accuracy, as well as to provide more tailor-made treatments with the development of molecule-specific therapies.

Treatment

Unfortunately, there is yet to be an effective treatment for FTD and related disorders in spite of the recent progresses in molecular genetics sparking various trials on drug targets, animal models and early stage compounds bordering on the realm of definitive clinical trials (Boxer et al., 2013a & 2013c). As for existing pharmacological treatment options, the list of trial-tested symptomatic treatments may appear wanting, nonetheless it is what we have from evidence available – interested readers are encouraged to read up on the relevant literature for details (Karageorgiou & Miller, 2014). The target population in most drug trials is the bvFTD group. In general, selective serotonin reuptake inhibitors (SSRIs) appear to be associated with some benefits in behaviour and compulsions. Cholinesterase inhibitors not only have no benefit, but may also worsen behavioural disturbances. The use of memantine is not supported in recent trials though it is well tolerated (Boxer et al., 2009, Boxer et al., 2013b, Vercelletto 2011); and atypical antipsychotics should be used with caution due to their side effect profiles.

The disappointment in current drug therapies dictates that the first-line therapy for behavioural disturbances in FTD remains non-pharmacological (Merrilees, 2007; Perry & Miller, 2001; Talerico & Evans, 2001). This is optimally provided by a multidisciplinary team (Karageorgiou & Miller, 2014). Examples include but are not limited to caregiver education, communication enhancement, exercise and physiotherapy, interventions to minimize undesired behaviour, regular activity and sleep schedule, respite and support, etc. (Riedijk et al., 2006; Talerico & Evans, 2001; Weintraub & Morhardt, 2005),

Non-Pharmacological Treatment – Case Illustration

The two case vignettes below outline the approach, which is but one of many possible lines to take, employed by the authors' team on non-pharmacological treatment in FTD. Here we follow the principle of identifying clinical symptoms, recognizing underlying cognitive signs, eliciting and capitalizing on preserved

strengths and applying strategic interventions to cater for the specific needs of FTD clients and their caregivers (Yan, Tsoh & Law, 2016).

Case 1: A bvFTD case

Brief History: A 52-year-old retired hospital health care assistant first presented with insidious memory deficits and behavioural change. She was unable to work as she forgot the instructions given and displayed odd behaviour (e.g. massaging deceased patients' bodies). She appeared restless and anxious, kept on repeating the same phrases over and over ("she was old and could not recall", "it's all over"), idled in the streets and crossed roads regardless of traffic and displayed increasing disturbing behaviour (e.g. inappropriate laughter, spitting, etc.). Her family found her unmanageable and sought help. Family history: the patient's mother suffered from memory problems in her sixties without formal diagnosis.

Clinical symptoms: Odd behaviour, verbal stereotypy, distractibility, restlessness, limited social interaction, poor judgment, labile affect, lack of insight

Cognitive profile: MMSE (on first presentation) 17/30. Poor initiation, perseveration, mental rigidity, stimulus - bound behaviours, nominal aphasia

Strengths: Preserved procedural memory, preserved visual memory and gross perceptual and visual spatial skills. Ability to comprehend written instructions

Neuroimaging: MRI (2 years after onset): unremarkable. SPECT (5 years after onset): perfusion deficit pattern involving bifrontal-temporal and left parietal lobes, suggestive of frontotemporal dementia.

Strategic interventions:

(1) Identifying strengths, engaging in meaningful activities, using visual cues, setting up tasks with demonstration (e.g. laying out cleaning utensils in a room in the day hospital, the client then started doing cleaning tasks and remained engaged for 45-60 minutes, during the time the stock phrases were spoken only occasionally);

(2) Education and skill transfer for home programmes, establishment of structured daily routines (e.g. collaborating with patient's family on home tasks) and making use of her "rigidity" to further consolidate and sustain such routines once these became more like a habit.

Outcome: The patient became much less restless and could be engaged in meaningful daytime activities with reduced caregiver stress; for example preceding the intervention she could only sustain 20 minutes' attention on simple tasks like knitting; after she was treated she was could be engaged to perform complex household tasks for the whole morning or afternoon (she did not lose the capabilities for these and other activity-of-daily-living (ADL) tasks in the mild to moderate stage of her dementia, it was her high distractibility and her other executive dysfunctions that precluded her from properly carrying out these tasks). She even slept better, likely from the enriched, structured daytime activities. She was able to be stably maintained for 5-6 years in community living with much better coping by the family members before physical deterioration and fall risks which necessitated a residential placement for her.

Case 2: A svPPA case

Brief history: A 64-year-old housewife was referred from GP for "dizziness" and "anxiety". Patient reported "lacking confidence and needing reminders (e.g. shopping list and other written aids)", she forgot people's names, could not follow conversations and respond appropriately, had "dizziness in her head" and her "mind went blank", and also took

a long time to name common objects. No psychosocial stress prior to these difficulties. Functioning was relatively preserved with the aforementioned compensatory methods. History taking appeared to be difficult; she often had apparent difficulties finding the words or phrases to accurately describe her ideas. Supplementary information was collected from collateral informant (husband). Husband reported the patient had "3-4 years of anxiety" and "frequent complaints of dizziness and forgetfulness"; he believed "she only forgot things when she was anxious" – while patient said "she was only anxious when she couldn't complete tasks" and was further frustrated by husband's criticisms (e.g. "too lazy to remember things", "too dependent", "lacked interests and hobbies for stimulation"). The team's initial impression was that it was unlikely a straightforward case of Generalized Anxiety Disorder (GAD); underlying cognitive impairments were suspected. Dementia work-up (to rule out reversible causes) results were negative. A trial of SSRI resulted in some improvement in mood; however, the cognitive symptoms persisted and some functional decline was noted; therefore she was given the provisional diagnosis of presenile-onset dementia 6 months after presentation and referred for further assessments accordingly. A year after that, positive signs were elicited in frontal lobe tests and thus she was referred for in-depth assessment and intervention at the Psychogeriatric day hospital.

Clinical symptoms: Anxious mood, language and memory impairments, frustration when unable to communicate or when chided by family members

Cognitive profile: Nominal aphasia (especially nouns), marked word-finding difficulty, poor cognitive flexibility and poor working memory. Six months after the first presentation: The Rivermead Behavioural Memory Test (RBMT) showed deficits in both immediate and delayed recall; MMSE (on presentation) 15/30, 6 months later, and 16/30, another 12 months later 17/30; Hierarchy Dementia Scale (HDS) 1.5 years from first presentation was 135/200. Results of the Chinese Frontal Assessment Battery (cFAB) 2.5 and 3 years after the first presentation were 6/18 and 3/18 respectively, which indicated gross impairments of frontal executive functions.

Strengths: Preserved visual memory, ability to employ compensation techniques and ability in mother tongue

Neuroimaging: CT brain (1 year after presentation) showed mild generalized loss of volume in left cerebral hemisphere; MRI/MRS (21 months after presentation) showed mild generalized decrease in volume of the left cerebral hemisphere, including around the sylvian fissure in Broca and Wernicke areas. Combined with clinical presentation the overall clinical features were suggestive of primary progressive dysphasia (PPA). Brain perfusion scan (2 years from presentation): Cerebral SPECT shows typical primary progressive aphasia pattern.

Strategic interventions:

(1) Education to patient and caregiver on cognitive deficits, naturalistic observation of cognitive assessments by family members, explanation of misconstrued cognitive signs (e.g. that the patient was not "too lazy" or "too dependent" to remember as they have thought; it was her language impairment due to her FTD that affected her ability to name objects or names, etc.).

(2) Exploration of compensatory coping strategies (e.g. use of picture cards), design cognitive stimulation tasks, and caregiver participation in training with visual cues (e.g. on common objects);

(3) Encouragement of positive (e.g. validation of patient's vexations) and effective

communication (e.g. demonstration of the tasks concerned instead of complex verbal instructions);

(4) Implementation of home programmes (e.g. training on tablet computer), adjusting difficulty of home tasks and day care centre activities (as patients like her would be reluctant to participate if these were too challenging) and encouraging furthering on tasks that she could complete (e.g. colouring) with a sense of positive fulfilment.

Outcome: The patient's anxiety was much reduced, the caregiver was more tolerant (e.g. husband offered verbal guidance in patient's dialect during training), carergiver stress was reduced, and the relationship and communication between the patient and the caregivers improved significantly. Four years after the patient's first presentation, the patient's son eventually took our advice and helped initiate and design a list of training items tailor-made for the patient in the form of cue cards (e.g. favourite fruits, facial expressions to express herself, pictures to indicate her needs, etc.) in collaboration with our occupational therapists to prepare and train the patient on overcoming the language deficit as her cognitive and language abilities further deteriorated. The patient was well maintained in the community with support from a day care centre and could still function at home with her family's assistance in the 2 years that followed when we last seen her.

Conclusion

This article reviews the updated literature on frontotemporal lobar degeneration (FTLD) and clinical syndromes of frontotemporal dementia (FTD) on epidemiology, diagnosis and treatment. In addition, the authors shared their team's approach towards non-pharmacological treatment in FTD with two local case vignettes with the wish to beget more fruitful discussions on strategies to handle the clinical symptoms and enhance the quality of life of persons with FTD when no curative treatments are available.

摘要

額顳葉認知障礙症新知及本地個案研究

本文描述有關「額顳葉認知障礙症」的一些最新的醫學理解(包括流行病學調查，診斷和治療等方面)。這方面的資訊來自近期的醫學文獻，以及二零一六年九月份的一個大型國際額顳葉認知障礙症會議中公開發表的資料。另外作者用兩個個案的型式，介紹了一些可行的非藥物性治療方法，希望能和讀者引起有關的討論，目的是在目前沒有藥物能夠根治此病或減慢病程進度的情況下，一起研究能夠有效控制病徵帶來的困擾，以及改善患者生活質素的辦法。這病症患者通常在六十歲左右開始發病；因為人口在本地和世界各處均邁向老化，患者的數目正大幅增加，因此增加對於額顳葉認知障礙症各方面的理解，實在是刻不容緩的。

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