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Frontotemporal Dementia in Eight Chinese Individuals

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Abstract

Frontotemporal dementia (FTD) has rarely been reported in Chinese populations. There are many potential reasons for this, including possible hesitancy on the part of patients or families to bring FTD-related symptoms to medical attention. Here, we present data on eight Chinese individuals, all of whom met criteria for the behavioral variant of FTD or the semantic variant of primary progressive aphasia. These patients presented for neurological evaluation at a relatively advanced stage. The mean MMSE score at initial presentation was 15. Behavioral symptoms were common and usually elicited during the medical history only after direct questioning. Delay in presentation was attributed to a variety of issues, including family disagreements about whether the symptoms represented a disease and lack of medical insurance. These cases illustrate that the symptoms of FTD in Chinese Americans are similar to those in Caucasians but various factors, some potentially culturally-relevant, may influence the likelihood and timing of clinical presentation for FTD, as well as other dementias. Additional study of FTD in diverse ethnic groups needs to address barriers to clinical presentation, including factors that may be culturally specific.

Keywords

Frontotemporal dementia; Chinese; ethnic culture; pathology; cognitive impairment; behavior changes

Introduction

Frontotemporal dementia is a term that represents a group of disorders that are often overlooked as a cause of dementia. Unlike Alzheimer's disease (AD) in which memory and visuospatial symptoms are common presenting features, FTD is characterized by early behavioral changes or language deficits. There are three subtypes of FTD: behavioral variant of frontotemporal dementia (bvFTD), and two disorders presenting as primary progressive

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aphasia (PPA), including a progressive non-fluent variant (nfvPPA), and a semantic variant (svPPA) (Gorno-Tempini et al., 2011; Neary et al., 1998; Rascovsky et al., 2007; Rascovsky et al., 2011). Estimates of the prevalence of FTD vary between 5% and 15%, but FTD is a particularly important cause of dementia in patients below the age of 65, being at least as common as AD in this group (Ratnavalli, Brayne, Dawson, & Hodges, 2002; Rosso et al., 2003; Stevens et al., 2002).

Most of our knowledge about atypical neurodegenerative diseases such as FTD comes from the study of non-minority populations. Among minority samples, FTD is infrequently reported. Asian Americans comprise one of the fastest growing population groups in the United States and, among Asian Americans, Chinese Americans make up the largest group, representing 23% (http://www.census.gov/acs/www/). Although dementia in minority communities is receiving more attention, Chinese Americans are still under-represented in tertiary care dementia clinics and in research studies on dementia (Hinton, Guo, Hillygus, & Levkoff, 2000; Hou, Yaffe, Perez-Stable, & Miller, 2006; Lombardo, Wu, Hohnstein, & Chang, 2002; Wu, Lombardo, & Chang, 2010). The available evidence suggests that neurodegenerative disorders such as AD and FTD may be diagnosed less often or later in their course in Chinese individuals compared to Caucasians (Chen & Hu, 2006; Hou, et al., 2006; Sheng, Law, & Yeung, 2009). Cultural factors could contribute to this. In many cultures, the cognitive symptoms of dementia are attributed to normal aging, so that a medical evaluation may not be sought. One study found that African-American, Chinese, and Latino caregivers of family members with AD all share the initial impression that memory loss was not important enough to address in clinical settings (Mahoney, Cloutterbuck, Neary, & Zhan, 2005). In the Chinese culture, symptoms of dementia may also be interpreted as normal and inevitable (Ikels, 1998). Stigma around dementia as a mental illness may also delay or prevent diagnosis (Hinton, et al., 2000; Yeo, Gallagher-Thompson, & Lieberman, 1996)

Consistent with the relative underrepresentation of Chinese Americans in dementia research cohorts, published reports of FTD in Chinese people are very rare. Yet, there are reasons to believe that FTD is at least as prevalent in individuals of Chinese descent as it is in other ethnic groups. A study examining the prevalence of FTD in patients seen at the State of California Alzheimer's Disease Centers found that FTD was as common in Asians and Pacific Islanders as in Whites (Hou, et al., 2006). Genetic studies have revealed that the H1 haplotype of the microtubule-associated protein tau (MAPT) gene, which is a risk factor for FTD-related pathology (Cairns et al., 2007), is more common in non-European than in European populations (Evans et al., 2004). Furthermore, the apolipoprotein E (APOE) ε2 allele, which may be protective against AD, is more prevalent than APOE ε 4 in Chinese individuals (Hallman et al., 1991). These genetic findings suggest that minorities including Asians and Pacific Islanders may be at a higher risk of developing FTD, as opposed to other types of dementias, compared with individuals of European ancestry.

The near absence of reports of FTD in Chinese populations invites speculation that cultural or linguistic factors may cause the disorder to present in an atypical manner in Chinese individuals compared with FTD cases in other ethnic groups. Alternatively, the fact that FTD presents primarily with behavioral features seen in psychiatric illnesses may lessen the likelihood that it would be brought up with a physician because of the stigma associated with psychiatric illness in the Chinese culture (Cook & Wang, 2010; Yeo, et al., 1996). This paper describes the clinical and neuropsychological presentation of eight Chinese individuals diagnosed with FTD. These cases emphasize that, while FTD occurs in Chinese people and presents with the typical behavioral and language features, FTD is similar to other dementias in being brought to medical attention relatively late in its course in Chinese

individuals, raising concerns that cultural or other factors may delay recognition of this disorder.

Materials and Methods

As part of an effort to increase participation of Chinese elders in research on cognition in aging, the University of California, San Francisco (UCSF) maintains an outreach program aimed at the San Francisco Chinese community that has recently been described in detail (Chao et al., 2011). The program, in place since 2004, is staffed by Chinese-speaking coordinators and maintains contact with physicians serving this community to encourage referrals. Most of the individuals with cognitive complaints evaluated through this program are referred by physicians and evaluated either at sites in San Francisco's Chinatown, or at UCSF's Parnassus Heights campus. Nearly 500 individuals have been evaluated to date.

The evaluation includes history and physical with informant interview and functional assessment, and cognitive assessment. Behavioral symptoms are elicited through the clinical history. The Neuropsychiatric Inventory (NPI), a caregiver based assessment of behavior validated for use in Chinese (Cummings, 1997; Leung, Lam, Chiu, Cummings, & Chen, 2001), is also collected in both English and Chinese speaking participants. Functional impairment is assessed via the clinical history and quantified using the Clinical Dementia Rating Scale (CDR, (Morris, 1997)).

All patients are asked whether they would feel more comfortable being tested in English or Chinese. For those tested in English, we use a previously described battery of tests that provides an assessment of memory, executive function, language, and mood (Kramer et al., 2003). Briefly, this includes the MMSE (Folstein, Folstein, & McHugh, 1975), the California Verbal Learning Test (D. C. Delis, Kramer, Kaplan, & Ober, 2000), digit span backwards, a copy of a complex figure, memory of a figure after 10 minutes, confrontational naming (15 items from the Boston Naming Test (Kaplan, Goodglass, & Wintraub, 1983), a brief syntax comprehension task, a set-shifting task (modified version of the Trails B task (Reitan, 1958)), and tests of verbal and non-verbal fluency (design fluency (D. Delis, Kaplan, & Kramer, 2001)). For those opting to be tested in Chinese, we use the Chinese version of the Cognitive Abilities Screening Instrument (CASI-C). This battery is scored from zero to 100 and provides as a broad assessment of cognition, including recent and remote memory, attention and concentration, visuospatial ability (figure copying) and naming and comprehension abilities (Lin et al., 2002; Liu et al., 1994). In addition, episodic memory is tested in Chinese using the Common Objects Memory Task, a list learning task that has been used across cultures (Kempler, Teng, Taussig, & Dick, 2010). Working memory is assessed using forwards and backwards digit span.

For the purposes of this report, the severity of behavioral and language problems were rated on a four point scale according to the clinical history, along with ancillary neuropsychological data for some of the language symptoms (see Table 1 for rating scale). Cognitive impairments were also rated on a four point scale, based on comparison of scores to available norms, to simplify comparison across the Chinese and English batteries (Table 2).

Results

Through the UCSF Chinese outreach program, eight Chinese individuals, all referred for evaluation by physicians, were identified as having frontotemporal dementia; four had bvFTD and four had svPPA (Table 1). BvFTD patients exhibited typical behavioral symptoms including disinhibition, apathy and obsessive preoccupations, and svPPA patients

exhibited loss of word and object knowledge, but also frequently showed significant behavioral symptoms similar to bvFTD. The bvFTD patients would meet recently published criteria for probable bvFTD (Rascovsky, et al., 2007) and the svPPA patients would meet recently published criteria for this disorder (Gorno-Tempini, et al., 2011). There was some evidence based on the clinical interactions that behavioral symptoms were not at the forefront of the family's complaints, even though they were quite significant. In case one, more than eight years of bad judgment and disinhibition were tolerated before medical attention was sought. This led to catastrophic consequences for the family. In all eight individuals there was a tendency to focus on cognitive and motor symptoms during the clinical history, and behavioral complaints were elicited only secondarily with direct questioning.

The mean duration from symptom onset until presentation was 5.3 (±2.5) years, and it ranged between 3 and 10 years. The longest durations (8 and 10 years) were seen with bvFTD. At the time this case report was being prepared, families of these patients were contacted to assess the reasons for treatment delays. Four families were able to be contacted, revealing a variety of reasons. In case 1, the family reported that disagreement within the family about whether these symptoms represented a change in personality prevented them from seeking medical attention. For Case 4, the family was not aware of cognitive or behavioral changes, and physicians became concerned about dementia when a routine scan in an emergency department for dizziness revealed significant brain atrophy. For Case 6, the family felt that forgetfulness was normal, and did not bring the issue to medical attention until the patient became nearly mute. When medical evaluation was pursued, the patient was diagnosed with AD, and the diagnosis was not changed until evaluation at UCSF. For case 8, the patient lived alone in China and moved to the US during the early phase of the illness, and did not have medical coverage for several years, preventing medical assessment.

Since being seen, three patients have died, but our staff was only contacted about Case 1, who received an autopsy (see below).

Below we provide histories for two illustrative cases.

Case 1, bvFTD

A 57-year-old right-handed Chinese man was evaluated for behavioral changes over eight years. He was born in Hong Kong and immigrated to the U.S. 31 years prior to evaluation. He received 12 years of education and worked as a chicken farmer. His primary language was Cantonese (Chinese) but he also spoke English as a second language. He became more outgoing and prioritized his participation in Chinese social groups over his family activities. To his family's surprise, he chose to attend a party rather than his daughter's final music recital. He flirted with teenage girls and cheated during a school raffle. At age 51, he lost interest in the family business, and his family was forced to sell their farm. He obtained a new job, but was let go within one year due to his tardiness and inability to follow instructions. Over the next five years, he became disinhibited and compulsive. He frequently sang in public, and his driving became reckless. He was arrested for failure to stop for a police car and lost his driver's license. He became more apathetic, and had no insight into his behavioral changes. He developed a preference for sweets and fast foods, eating daily at McDonald's or Kentucky Fried Chicken. Two years prior to evaluation, he exhibited word finding difficulty and trouble with language comprehension in both Cantonese and English. His ability to recognize the faces of people he knew deteriorated. No visuospatial symptoms were noted. He could not live independently and was not able to handle his finances. There was no family history of neurological or psychiatric disorders.

Neurological examination was unremarkable.

A brain MRI scan showed prominent frontal and anterior temporal lobe atrophy. The clinical diagnosis was bvFTD.

One year later, his MMSE declined to 3/30. He died at age 58 due to alcohol-related illness. Autopsy showed cortical atrophy in the frontal and temporal regions, right greater than left. Pick bodies were found in the dentate gyrus of the hippocampus and other cortical regions. There were no neuritic plaques, and no Lewy bodies. The neuropathological diagnosis was Pick's disease.

Case 2, svPPA

A 67-year-old right-handed Chinese man was evaluated after 6 years of language difficulty. He was born and college-educated in the U.S. He worked in food preparation from the age of 10 until he began to invest wisely in real estate. After a planned early retirement, he was found to be confused by conversations and instructions from his wife. His language became riddled with semantic paraphasic errors and he began to express complex recurrent utterances, with a story-like quality. He stopped cooking, and developed difficulty recognizing food items but began to hoard food and consume more sugar-laden items. He became fixated on a buffet restaurant and frequently overate at the buffet even after claiming to be full, gaining 20 pounds over a few years. He began to sing when attempting to engage strangers. His family recognized the value of this developing compulsion and arranged for him to perform weekly at a senior center as the song leader. There were no motor or visuospatial symptoms. He needed assistance with most of his basic activities of daily living. There was no family history of neurological or psychiatric disorders.

On examination, he was highly energetic, with pressured speech. His recurrent utterances demonstrated semantic paraphasic errors. He was easily distracted and had aberrant motor behaviors including pacing and picking at clothing. He did not follow instructions during the neurological examination, but there were no cranial nerve or motor deficits identified.

MRI of the brain showed profound left greater than right temporal atrophy with minimal orbitofrontal atrophy. PET scanning with the Pittsburgh B compound, which labels neurofibrillary amyloid plaques in vivo (Quigley, Colloby, & O'Brien, 2011), was normal. He was clinically diagnosed with svPPA.

Two years later he was re-evaluated, and he had continued to lose vocabulary in addition to having increasing difficulty comprehending verbal commands. He relied on "body language" to communicate. He had no motor symptoms. He remained an excellent navigator and had no deficits in recognizing familiar faces.

DISCUSSION

Dementia research in Asia has focused on AD and vascular dementia, (Chiu & Zhang, 2000; Liu et al., 1998; White et al., 1996) while FTD in Asian and Pacific Islander populations has not been studied extensively. This paper describes eight Chinese individuals with FTD. Four exhibited significant behavioral changes prior to age 65 and met criteria for bvFTD. The other subjects presented with semantic loss and met criteria for svPPA, and also developed significant behavioral problems. These eight cases were identified through an ongoing program dedicated to encouraging more Chinese Americans to participate in dementia research, and they represent about 6% of the approximately 140 individuals diagnosed with dementia through this program, a prevalence that is in the lower end of the range of estimates of FTD prevalence (Ratnavalli, et al., 2002; Rosso, et al., 2003; Stevens, et al., 2002). Given that UCSF receives frequent referrals for FTD, it is difficult to compare this number to other studies based on population data, but this number is generally consistent

with prior studies suggesting that the prevalence of FTD in Chinese Americans is similar to that in Caucasians (Hou, et al., 2006). Most individuals presented for medical evaluation at a relatively advanced stage. The average MMSE was 15, which is substantially lower than the MMSE scores reported at presentation in previously published series of patients with FTD (Johnson et al., 2005). The average disease duration was 5.3 years prior to presentation, which is longer than previous reports for FTD (Pijnenburg, Gillissen, Jonker, & Scheltens, 2004). The findings in these cases are consistent with other studies of Chinese individuals that have documented relatively low levels of cognitive performance at first presentation for dementia care (Sheng, et al., 2009) and they suggest that, although FTD presents similarly in Chinese and Caucasian individuals, factors yet to be precisely identified may lead to late diagnosis or under-diagnosis of FTD as well as other dementias.

For most lay persons, the cognitive symptom most closely associated with neurodegenerative diseases is memory loss. Thus, among cognitive symptoms, memory impairment is most likely to be perceived as a potential medical ailment (Cummings, Vinters, Cole, & Khachaturian, 1998). In contrast, symptoms such as hallucinations, disinhibition, and apathy may be difficult to interpret as biologically-related symptoms. A Chinese idiom “Fan Lao Huan Tong” describes child-like behavior in the elderly such as throwing a tantrum or saying “silly” things. This idiom has no negative connotation, suggesting that child-like behavior in the elderly is to be expected. Other widely accepted Chinese cultural explanations of behavioral symptoms include an imbalance in yin-yang, bad feng shui, or punishment for past wrongs. These explanatory models suggest that Chinese individuals may not find medical consultation relevant in treating behavioral symptoms related to dementia. Indeed, prior studies have indicated that Chinese caregivers are less distressed about neurobehavioral symptoms than Caucasian caregivers (F. C. Pang et al., 2002). Even if symptoms are recognized as a potential mental illness, cultural factors can lessen the likelihood that they will come to medical attention. Mental illness is extremely stigmatizing and considered shameful in the Chinese culture (Cook & Wang, 2010; Yeo, et al., 1996). Dementia has been traditionally translated as “crazy and catatonic disorder” in Chinese. As a result, Chinese individuals may be less likely to discuss potential mental disturbances with individuals outside of the family, particularly with physicians of a different race or cultural background. Clinical consultation may be sought only when the behaviors become unmanageable. In a cross-cultural study comparing neuropsychiatric symptoms in Chinese with AD in Hong Kong and Taiwan with Caucasians in Los Angeles, the Chinese with AD had higher Clinical Dementia Rating and neuropsychiatric inventory scores at initial evaluation. The study also indicated that memory loss, not behavioral disturbance, was the most common chief complaint by Chinese caregivers (S. M. Pang et al., 2003). These findings support the idea that dementia must be more advanced before being brought to medical attention in Chinese compared with Caucasian populations, and even then the neuropsychiatric symptoms may be downplayed. This was reflected in our experience as well, because behavioral symptoms were only elicited on direct questioning.

While this case series suggests that FTD presents in Chinese individuals similarly to the way it presents in Caucasians, the relatively late presentation in these individuals raises concerns that cultural issues such as the ones discussed above may delay the referral of FTD patients for medical attention. The available information from these individual cases does not point clearly to a particular reason for late presentation; rather, a variety of reasons were identified. One patient born in the U.S. still had a six year delay until subspecialty evaluation, raising doubt about the role of culturally influenced biases in this case. In another case the family felt that forgetfulness is a normal part of aging. Notably, this patient presented with word finding difficulties, which are a common complaint in older individuals, and was diagnosed with svPPA, highlighting the possibility that svPPA may be particularly amenable to this type of interpretation. In a third case, lack of medical insurance

was an important contributor. In the fourth case, family disagreement was a major contributor, but the precise influence of cultural beliefs could not be detected in discussions with the patient's family. These cases illustrate that there are many potential barriers delaying clinical presentation. Without systematic assessment of cultural beliefs and other relevant factors in the appropriate cohorts (i.e. older Chinese-Americans and their family members) it is difficult to quantify the degree to which culture influences the timing and likelihood of presentation.

It is notable that only one of the families of the three individuals who died consented to autopsy. Clinically diagnosed FTD is associated with a variety of pathologies (Seelaar, Rohrer, Pijnenburg, Fox, & van Swieten, 2011), including AD pathology in about 15% to 20%, and most of these specific pathologies cannot currently be differentiated in life using biological markers. Thus, autopsy is still a critical aspect of FTD research. The 33% autopsy rate (1 of three who has died) in this small sample of FTD patients is different that the autopsy rate in the general FTD cohort at UCSF, which is over 80%. This reflects our overall experience at UCSF that Chinese participants are less willing to consent to autopsy than Caucasian research participants. Again, cultural influences may be relevant, but there is relatively little data about this. One study found that a mixed sample of Asian Americans (Japanese, Chinese, Filipino) had more negative attitudes toward organ donation and more frequently identified body integrity after death as important compared with Caucasians (Cheung, Alden, & Wheeler, 1998). There have been no studies specifically regarding Chinese individuals and the issue of brain donation for diagnostic or research purposes, particularly in the setting of aging and dementia research.

The issues raised by this study, including the possibility that non-Caucasians are at increased risk for late clinical presentations of dementia, maybe particularly with FTD, indicates that more research needs to be done on culturally specific barriers preventing early clinical presentation. In the meantime, substantial efforts need to be made to educate and reach out to these populations and the physicians who serve them to facilitate earlier diagnosis. These educational efforts should include the information that psychiatric disorders and personality changes late in life could be a neurological disease, and should be evaluated appropriately. Prior studies indicate that educational programs can be effective in changing clinical practice (Lombardo, et al., 2002).

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Table 1

Summary of clinical symptoms in eight cases of FTD[1]

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Years in U.S.[2]	31	US born	N/A	33	N/A	5	26	5
Gender	Male	Male	Female	Male	Female	Female	Male	Female
Education (years)	12	16	16	16	9	?	18	10
Age at evaluation	57	67	67	73	67	74	65	70
Illness Duration[3]	8	6	4	4	3	3	4	10
Family history	–	–	–	–	–	–	–	–
Initial symptoms	Gregarious Neglecting family	Trouble understanding Conversations Instructions	Word finding problems	Word finding problems	Loss of interest in job, family	Word finding problems	Wandering Loss of embarrassment	Obsessive routines
Memory loss	+	++	+	–	–	+	+	+
BvFTD Clinical Features[4]								
Disinhibition	+++	+++	–	+	–	+	++	+++
Apathy/Inertia	++	++	++	–	++	++	++	++
Loss of empathy	+++	–	–	–	+	–	–	+
Obsessions/compulsions	+	++	+	++	+	++	++	+++
Dietary changes	++	++	–	–	++	–	+	+++
SvPPA Clinical Features[5*]								
Impaired naming	++	+++	+++	+++	+	+++	+	+
Impaired word recognition	+	++	+	+	–	++	–	–
Impaired object knowledge	–	++	+	–	–	++	–	–
Clinical diagnosis	bvFTD	svPPA	svPPA	svPPA	bvFTD	svPPA	bvFTD	bvFTD
Imaging Findings	MRI bilateral frontal, temporal atrophy	MRI L>R temporal atrophy, PiB negative	MRI R temporo-parietal atrophy	MRI L temporal atrophy	MRI R>L temporal atrophy, PiB negative	MRI L temporal atrophy	MRI bilateral frontal, temporal atrophy	CT R temporal and frontal atrophy
Current status[6]	Deceased	?	?	Deceased	?	Living	Deceased	Living
Autopsy results	FTD, Pick's Dz.	N/A	N/A	Not performed	N/A	N/A	Not performed	N/A

[1] Ratings based on clinical assessment of severity from the clinical history and available neuropsychological data: + = present, not affecting function, ++ = some effect on function, +++ = significant effect on function.

[2] N/A = Not applicable. These patients were not U.S. residents, but were evaluated on visits to the U.S.

[3] Prior to presentation at UCSF, in years

[4] Key clinical features from recently published criteria for bvFTD, which required early development of specific features (Rascovsky et al., 2011)

[5] Key clinical features from recently published criteria for svPPA (Gorno-Tempini et al., 2011)

[6] ? = current status unknown

[*] includes surface dyslexia as a criterion, which is not relevant in Chinese

Table 2

Summary of neuropsychological data[1] in eight cases of FTD

	Case1	Case2	Case3	Case4	Case5	Case6	Case7	Case8
Testing Battery[2]	MAC	MAC	CHB	MAC	MAC	CHB	CHB	CHB
MMSE	22	7	14	19	16	23	7	10
CASI Score	ND	N/A	50	N/A	N/A	78	N/A*	25
Episodic Memory[3]	++	+++	+++	+++	+++	+	+++	+++
Naming[4]	+++	+++	+++	+++	++	Intact	Intact	+
Syntax Comprehension	++	Intact	Intact	+++	Intact	Intact	++	+
Visuospatial Function[5]	Intact	Intact	Intact	Intact	Intact	Intact	Intact	+++
Backwards Digit Span	4 (Intact)	3 (+)	5 (Intact)	4 (Intact)	4 (Intact)	5 (Intact)	2 (++)	UT
Other Executive[6]	+++	+++	Intact	+++	+++	Intact	+++	UT

[1] Ratings of severity based on performance on domain specific tasks compared with established norms. + = > 1 SD from norm, ++ = 1–2 SD from norm, +++ = >2 SD from norm. ND = test not done. UT = untestable because of poor cooperation.

[2] MAC = Standard Memory and Aging Center Battery, CHB = Battery used for Chinese speaking patients (see Methods)

[3] For MAC battery California Verbal Learning Test, for CHB CASI memory and Common Objects Memory Test

[4] For MAC battery, Boston Naming Test, for CHB, naming on CASI and Common Objects Memory Test

[5] For MAC battery, copy of complex figure, for CHB, copy of figures from CASI

[6] For MAC battery, Modified Trails, for CHB, attention and concentration from CASI

* Because of very low functioning, this person did not undergo the full CASI, only select testing, including a Chinese version of the MMSE