Published in final edited form as:

Alzheimer Dis Assoc Disord. 2009 ; 23(1): 77–81. doi:10.1097/WAD.0b013e318182d874.

Difficulties in detecting behavioral symptoms of frontotemporal lobar degeneration across cultures

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Abstract

Cross-cultural studies of neurodegenerative disorders are especially important when the disease in question is difficult to diagnose, particularly if symptoms of the illness include behavioral disturbances that may be interpreted differently in different cultures. One such disease is frontotemporal lobar degeneration (FTLD), an early-age-of-onset dementia that disproportionately affects social behavior. We report the demographic and neuropsychological characteristics of more than 300 patients diagnosed with FTLD in the United States (US), Greece and Turkey. We find that patients with the frontal variant of FTLD (FTD) are diagnosed at an earlier age and report earlier symptom onset in the US, than in Greece or Turkey. Furthermore, neuropsychological measures indicate that at diagnosis, FTD patients in the US are less impaired than patients in Greece and Turkey. Patients with FTD in Greece and Turkey are diagnosed later in the disease, presumably because their behavioral symptoms are not easily detected by the medical system in these countries. Our study underscores the need to create culturally-appropriate indices of the behavioral symptoms of FTLD, so that patients may be diagnosed and treated at an earlier stage.

Keywords

diagnosis; frontotemporal dementia; neuropsychological measures progressive supranuclear palsy; cross-cultural

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Frontotemporal lobar degeneration (FTLD) is a progressive neurodegenerative disease affecting the frontal and anterior temporal lobes. Once considered rare, recent work suggests that frontotemporal lobar degeneration (FTLD) is a common cause for dementia, particularly in patients under the age of 70 years. FTLD's prevalence is similar to that of AD with 15 cases per 100,000 between 45- to 64-years^{1, 2}. Other studies suggest that FTLD accounts for up to 20% of all patients with degenerative dementias^{3, 4}. FTLD is often further subdivided into

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three subtypes, based upon differences in regional atrophy and symptom patterns. These three subtypes are: 1) progressive non-fluent aphasia (PNFA), in which patients primarily show deficits in verbal expression, and predominantly left-frontal atrophy 2) frontal-variant frontotemporal dementia (FTD), in which first symptoms are generally behavioral disturbances and atrophy is symmetrical and predominately frontal and 3) semantic dementia (SD) or temporal-variant frontotemporal dementia, in which patients gradually lose access to semantic concepts (ie, meanings of words) resulting from temporal atrophy.

To date, the bulk of the studies on the prevalence and demographic characteristics of FTLT have been limited to patient cohorts in the US and the UK ^{1, 2}. Here, we present demographic characteristics of over 300 patients with FTLT seen in research clinics in the US, Greece and Turkey. In addition, patients presenting with progressive supranuclear palsy (PSP), a related disorder, are described because PSP and some FTLT patients show similar clinical and pathological findings (tau inclusions). These two patients groups are distinguishable, however, when behavioral symptoms dominate the early clinical presentation, as is the case in FTD ⁵. Cross-cultural examination of FTLT is particularly important since this dementia is characterized by behavioral changes, and the interpretation and detection of such changes is likely to vary with culture. Therefore, by describing characteristics of FTLT in different cultures, investigators may gain insight into the core features of the disease, and aid physicians across borders identify and treat patients appropriately.

Methods

Patients

We assessed patients in clinics in California, Greece and Turkey. Comprehensive historical, neuropsychological, neurological and neuroimaging data were collected in a standardized fashion at memory clinics in San Francisco, California, Athens, Greece (2 clinics) and Izmir, Turkey. At the Memory and Aging Clinic in San Francisco, patients were recruited through an extensive referral process including tertiary centers across California. Patients are seen independently of their financial resources. The Turkish University Dementia Clinic is also a tertiary health care center. Patients were referred by either a neurologist from secondary health care centers or from internal medicine physicians or primary care physicians working in the private or public medical systems. In Greece, patients were recruited via two different clinics, both part of the public medical system: patients can come to the General Hospital in Athens without referral, while patients seen through the University Hospital (Eginition) are almost exclusively referred through their neurologist, psychiatrist or general practitioner. The directors of these clinics all have expertise and a special interest in FTLT and PSP and their clinics serve as specialized referral sites. In addition, the same criteria were used for diagnosis across the clinics, and the directors of both the Greek and Turkish clinics have spent time working and training at the Memory and Aging Clinic in San Francisco. They continue to collaborate with the San Francisco clinic and attend international conferences related to the diagnosis of FTLT.

Demographic characteristics included the age of disease onset, education, gender and age at diagnosis. To assess whether the relative numbers of patients with FTLT subtypes and PSP differed between countries, we used a chi-square test.

Diagnostic Criteria

Patients were diagnosed with FTLT using the 1998 consensus criteria ⁶. PSP diagnosis was based on the Litvan criteria ⁷.

Neuropsychological Measures

The Mini-Mental Status Examination (MMSE) was administered to all patients in the language of the country in which they were tested. In addition, patients in the US and Greece were also assessed using the Neuropsychiatric Inventory (NPI) ⁸ and the Clinical Dementia Rating Scale (CDR) ⁹. For the NPI, the total score and the caregiver distress scores were analyzed separately.

Data Analysis: Demographic Information

We performed 3 (country) $\times$ 4 (diagnosis: FTD, SD, PA and PSP) ANOVAs on three dependent measures: age at diagnosis, age at disease onset and education, with Tukey's HSD to further investigate significant effects. We also wondered whether gender differences between diagnoses would be similar between countries. Therefore, we first collapsed across countries to see if the diagnoses had different proportions of males and females. Then we performed chi-square analyses for each country to see if the effect was observed.

Data Analysis: Neuropsychological Measures

We performed another 3 (country) $\times$ 4 (diagnosis) ANOVA on initial MMSE scores, with Tukey's HSD post-hoc tests to further investigate the significant effects. For patients from Greece and the US, we performed a similar ANOVA on total NPI scores and caregiver distress, as well as CDR scores.

Results

Patients

We assessed 336 patients across three clinics. Table 1 shows the distribution of patients by country and diagnosis. All three countries had more patients with FTD than with SD or PA. In Greece, a greater proportion of the patients studied were diagnosed with FTD than in the US and in Turkey [$\chi^2(2) = 9.50, p < .01$]. In Turkey no patients with SD were diagnosed during the course of this study.

Demographic characteristics

Age at diagnosis—The ANOVA revealed a main effect of country [$F(2, 365) = 3.48, p < .05$] a trend towards an effect of diagnosis [$F(3, 365) = 79.01, p < .08$] and an interaction between country and diagnosis [$F(5, 365) = 2.28, p < .05$]. These results are shown in Figure 1. Whereas the age at diagnosis was not different in Greece or Turkey for different disorders or FTLT subtypes, in the US, patients diagnosed with FTD were significantly younger than patients with PSP and SD [Tukey's HSD, $p < .001$ for both].

Age at Disease Onset—The ANOVA showed a main effect of country [$F(2, 345) = 5.47, p < .01$] and a significant interaction [$F(5, 354) = 2.35, p < .05$]. These results are shown in Figure 2. Overall, patients in Greece reported a higher age of onset than those in the US [Tukey's HSD, $p < .001$]. As well, only in the USA were patients with FTD reported to have symptoms earlier than patients with PSP or SD. From these results, we suspected that there may be a difference in the amount of time that passes between the onset of symptoms and diagnosis in the different countries. Therefore, we performed an ANOVA on the difference between age at onset and age at diagnosis. We did find a significant main effect of country [$F(2, 353) = 35.21, p < .001$]. In the USA, the time between diagnosis and the report of first symptoms was greater than in either Greece or Turkey (Tukey's HSD: $p < .05$). These results are seen in Table 2.

Education—An ANOVA revealed a main effect of country on education [$F(2, 343) = 39.54, p < .001$] with all countries significantly different from each other [Tukey's HSD, $p < .001$]. Results are shown in Table 3.

Gender—First, we collapsed across countries to see if males or females were more likely to show each of the disorders. Via binomial tests, we found that FTD and PSP patients were more likely than chance to be males than females. To investigate whether this distribution varied by country, we performed chi-square analyses for each disorder. Here, we found no differences between the countries [$\chi^2(2) < 3.5$, $p > .1$]. The higher prevalence of males with FTD is in line with findings from other international studies¹⁰.

Neuropsychological Measures

Since there was a difference in education between countries, we included education as a covariate in our analyses of neuropsychological measures.

Initial MMSE score at Diagnosis—Our ANOVA showed a main effect of country [$F(2, 336) = 11.69$, $p < .001$], a main effect of diagnosis [$F(3, 336) = 17.74$, $p < .001$] and a significant interaction of diagnosis and country [$F(5, 336) = 3.72$, $p < .001$]. Post hoc tests showed that in the USA, only the SD and PSP patients differed in their MMSE scores ($p < .05$). In Greece, FTD patients showed higher MMSE scores than PA patients ($p < .05$). PSP patients also showed higher MMSE scores than both SD and PA patients ($p < .05$). In Turkey, PSP patients showed higher MMSE scores than both FTD and PA patients ($p < .05$) and FTD patients also showed higher MMSE scores than PA patients ($p < .05$). These results are shown in Figure 3.

CDR and NPI measures—To ensure sufficiently large group sizes, we restricted our ANOVA to patients with FTLT. We did not have NPI scores from patients in Turkey. With education as a covariate, we found a significant main effect of diagnosis on both NPI scores [NPI total: $F(2, 199) = 10.37$, $p < .001$; NPI Caregiver Distress: $F(2, 172) = 4.30$, $p < .02$]. We also found a trend towards an effect of country on NPI total [NPI total: $F(1, 199) = 3.5$, $p < .06$] and a significant effect of country on Caregiver Distress scores: $F(1, 172) = 6.27$, $p < .02$. Post-hoc tests showed that FTD patients showed higher total and caregiver distress scores than PA and SD patients [Tukey's HSD: all $p < .05$]. These results are shown in Figures 4a and 4b.

With education as a covariate, our ANOVA of CDR scores indicated a main effect of country [$F(1, 229) = 10.34$, $p < .001$] and a trend towards a significant interaction between country and diagnosis [$F(1, 229) = 2.62$, $p < .075$]. Post hoc tests showed that only in the USA, FTD patients showed higher CDR scores than both SD and PA patients [Tukey's HSD: $p < .05$]. Results are shown in Figure 5.

Discussion

Our cross-cultural comparison of patient characteristics has shown that patients diagnosed with FTD and the other FTLT subtypes are diagnosed at a younger age in the USA than in either Greece or Turkey. Only in the USA were patients with FTD younger than patients with other FTLT subtypes or PSP. Furthermore, even the reported age of onset of symptoms is higher in Greece and Turkey than in the USA, particularly for patients with FTD. These patients are much more likely to be diagnosed on the basis of behavioral symptoms that include social interactions, than are patients with PSP, PA or SD, who, in turn, are more likely to present with language or motor disturbances. Interestingly, however, the proportion of patients with each of the subtypes of FTLT, as well as the tendency for more FTD and PSP patients to be male, is equivalent in the USA and Greece. This observation suggests that the age difference is not simply due to a lower rate of incidence of the disease, or disproportionate numbers of one of the subtypes.

When we compared the amount of time between the reported onset of symptoms and diagnosis, we found that patients in the USA were more likely to report symptoms well before diagnosis than patients in Greece and Turkey. Previous research shows that in FTD, the first symptoms

are primarily behavioral in nature¹¹. Therefore, one may interpret these findings as suggesting that the initial behavioral symptoms of FTD are ignored, or are more likely to be accepted as a normal part of life in Greece and Turkey. In fact, when we compared patients seen in the outpatient clinic with patients in the inpatient (University) clinic in Greece, we found that patients that were seen in the outpatient clinic, who were usually self-referred, were older than patients seen in the inpatient clinic, who were generally referred by a neurologist or psychiatrist. These results further suggest that FTLT symptoms are less likely to be considered a medical issue in the general population in Greece.

Support for this hypothesis is also found in the neuropsychological measures that indicate that at the time of diagnosis, patients with FTLT in Greece and Turkey are more impaired than patients in the USA. Even though we included education as a covariate in the analysis, these differences were significant, refuting the possibility that education alone can account for the lower neuropsychological scores in Greece and Turkey. Scores on the MMSE are lower, and scores on the CDR are significantly higher in Greece. While the MMSE is known to be a fairly ineffective test of cognitive deterioration in FTLT, it is a reasonable indicator of general cognitive function, and among the most reliable neuropsychological measures across cultures. These effects are particularly striking in the FTD subtype, in which the detection of behavioral symptoms that impair social interactions is most important.

The effect that behavioral symptoms have on caregiver distress, however, is significant in both the USA and Greece: caregivers whose loved ones are afflicted with FTD report feeling more distress than those who care for patients with PA or SD. Given these findings, it seems that earlier detection of FTD may be critical in improving the outcome and reducing caregiver distress in FTD patients who live in Greece and Turkey.

This report highlights important similarities with regard to key features of FTD across three different countries and cultures. In particular, FTD is highly prevalent in clinics in the US, Turkey and Greece with expertise in this condition. Also, the male predominance for FTD seen in previous studies is confirmed in the US, Greece and Turkey. Similarly, stress in caregivers who take care of patients with FTD is high in all three countries. These similarities are encouraging with regard to future epidemiological research into FTD and related disorders. In Greece and Turkey, caregivers appear to be more likely to care for FTD within the family structure before seeking medical help. As better therapies emerge for FTD and related disorders, new strategies will be needed to educate the lay public and physicians regarding the medical implications of late-life behavioral syndromes, in all three countries.

Acknowledgments

We would like to thank all of the patients and their caregivers who participated in this study. We would also like to thank grants to Dr. Bruce L. Miller from the National Institute of Aging including a Program Project Grant (PO1AG19724), and an Alzheimer's Disease Research Center (P50-AG023501) a Network grant from the Hillblom Foundation (NIA) and a Fellowship grant from the McBean Foundation to Indre Viskontas. We would also like to thank Dr. C.E. Karageorgiou, Pr. D. Vassilopoulos and Pr. N. Kalfakis for their continued support.

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Figure 1.

Age at diagnosis by country. Mean age in years at diagnosis for each disorder. Error bars represent the standard error of the mean.

Figure 2.

Age at Disease Onset by Country. Mean age at disease onset for patients in each country. Error bars represent standard error of the mean.

Figure 3.
Initial MMSE score by diagnosis and country. Error bars depict the standard error of the mean.

Figure 4.
a and 4b. NPI scores by diagnosis and country. Error bars depict the standard error of the mean.

Figure 5.
CDR scores diagnosis and country. Error bars depict the standard error of the mean.

Table 1

Distribution of patients by country and diagnosis.

	lvFTD	SD	PA	PSP	Total
USA	80	47	13	33	173
Greece	72	24	16	7	119
Turkey	16	0	8	20	44
Total	168	71	37	60	336

Table 2

Time between Diagnosis and Disease Onset.

Country	Mean (years)	Std. Error
USA	7.474	0.341
Greece	3.572	0.434
Turkey	3.188	0.509

Table 3

Education by Country. Mean education (years) in each country.

Country	Mean (years)	N	Std. Error
USA	16.3	173	0.49
Greece	10.2	119	0.48
Turkey	7.4	44	0.58
Total	12.9	336	0.36