Prognosis of Patients with Behavioral Variant Frontotemporal Dementia Who have Focal Versus Diffuse Frontal Atrophy

Jin San Lee[a], Na-Yeon Jung[b]
Young Kyoung Jang[c,d]
Hee Jin Kim[c,d], Sang Won Seo[c,d,e,f]
Juyoun Lee[g], Yeo Jin Kim[h]
Jae-Hong Lee[i], Byeong C. Kim[j]
Kyung-Won Park[k], Soo Jin Yoon[l]
Jee H. Jeong[m], Sang Yun Kim[n]
Seung Hyun Kim[o], Eun-Joo Kim[b]
Key-Chung Park[a]
David S. Knopman[p], Duk L. Na[c,d,f,q]

[a]Department of Neurology, Kyung Hee University Hospital, Seoul, Korea
[b]Department of Neurology, Pusan National University Hospital, Pusan National University School of Medicine and Medical Research Institute, Busan, Korea
[c]Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[d]Neuroscience Center, Samsung Medical Center, Seoul, Korea
[e]Department of Clinical Research Design and Evaluation, [f]Health Sciences and Technology, SAIHST, Sungkyunkwan University, Seoul, Korea
[g]Department of Neurology, Chungnam National University Hospital, Daejeon, Korea
[h]Department of Neurology, Chuncheon Sacred Heart Hospital, Hallym University College of Medicine, Chuncheon, Korea
[i]Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[j]Department of Neurology, Chonnam National University Medical School, Gwangju, Korea
[k]Department of Neurology, Dong-A Medical Center, Dong-A University College of Medicine, Busan, Korea
[l]Department of Neurology, Eulji University Hospital, Eulji University School of Medicine, Daejeon, Korea
[m]Department of Neurology, Ewha Womans University Mokdong Hospital, Ewha Womans University School of Medicine, Seoul, Korea
[n]Department of Neurology, Seoul National University Bundang Hospital, Seongnam, Korea
[o]Department of Neurology, College of Medicine, Hanyang University, Seoul, Korea
[p]Department of Neurology, Mayo Clinic, Rochester, MN, USA
[q]Stem Cell & Regenerative Medicine Institute, Samsung Medical Center, Seoul, Korea

Received   December 14, 2016
Revised   May 15, 2017
Accepted   May 16, 2017

Correspondence
Duk L. Na, MD, PhD
Department of Neurology,
Samsung Medical Center,
Sungkyunkwan University
School of Medicine, 81 Irwon-ro,
Gangnam-gu, Seoul 06351, Korea
Tel   +82-2-3410-1233
Fax   +82-2-3410-0052
E-mail   dukna@skku.edu

Background and Purpose Only a few studies have investigated the relationship between different subtypes and disease progression or prognosis in patients with behavioral variant frontotemporal dementia (bvFTD). Since a localized injury often produces more focal signs than a diffuse injury, we hypothesized that the clinical characteristics differ between patients with bvFTD who show diffuse frontal lobe atrophy (D-type) on axial magnetic resonance imaging (MRI) scans versus those with focal or circumscribed frontal lobe atrophy (F-type).

Methods In total, 94 MRI scans (74 scans from bvFTD and 20 scans from age-matched normal controls) were classified into 35 D- and 39 F-type bvFTD cases based on an axial MRI visual rating scale. We compared baseline clinical characteristics, progression in motor and cognitive symptoms, and survival times between D- and F-types. Survival analyses were performed for 62 of the 74 patients.

Results While D-type performed better on neuropsychological tests than F-type at baseline, D-type had higher baseline scores on the Unified Parkinson's Disease Rating Scale (UPDRS) Part III. Evaluations of motor progression showed that the disease duration with motor symptoms was shorter in D-type than F-type. Moreover, the survival time was shorter in D-type (6.9 years) than F-type (9.4 years). Cox regression analyses revealed that a high UPDRS Part III score at baseline contributed to an increased risk of mortality, regardless of the pattern of atrophy.

Conclusions The prognosis is worse for D-type than for those with F-type. Shorter survival in D-type may be associated with the earlier appearance of motor symptoms.

Key Words frontotemporal dementia, frontotemporal lobar degeneration, magnetic resonance imaging, prognosis.

INTRODUCTION

Behavioral variant frontotemporal dementia (bvFTD) is the most common clinical syndrome of frontotemporal dementia (FTD) and it may have different subtypes: the pathological subtypes include tau, transactive response DNA-binding protein 43 kDa (TDP-43), and fused in sarcoma (FUS) inclusions,[1] while the clinical phenotypes can be dichotomized into disinhibited- and apathy-predominant types.[2] Neuroimaging studies have also revealed several anatomical subtypes.[3,4] However, only a few studies have investigated the relationship between these subtypes and disease progression or prognosis.[5-8]

We often encounter patients with bvFTD who show one of two patterns of frontal lobe atrophy on axial magnetic resonance imaging (MRI) scans: 1) diffuse frontal atrophy (D-type) or 2) focal or circumscribed frontal atrophy (F-type). However, little is known about whether the clinical manifestations and prognoses differ between D- and F-type patients.

Pick's disease (PiD) is characterized by marked circumscribed prefrontal lobe atrophy.[9] Based on previous neuroimaging studies, we presumed that 4R-tau-positive disorders such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) result in less prefrontal atrophy than in PiD.[10,11] Given that motor symptoms are more common in patients with CBD or PSP than in those with PiD,[11,12] we hypothesized that D-type patients are more likely to be associated with motor symptoms, while F-type patients are less likely to exhibit parkinsonism or motor symptoms. In addition, since there are often more focal signs for localized injury than for diffuse injury, we hypothesized that F-type bvFTD patients have a more favorable outcome than D-type patients.

The objectives of this study were 1) to classify patients with bvFTD into the D- and F-types based on axial MRI scans, and 2) to compare the baseline characteristics, progression in motor and cognitive symptoms, and survival time between these two groups.

METHODS

Participants
In total, 81 patients were retrospectively recruited from 8 dementia clinics across Korea. All patients enrolled in this study met the clinical criteria for probable bvFTD as proposed by the International Behavioural Variant Frontotemporal Dementia Criteria Consortium.[13] Of the 81 initial patients, 2 with motor neuron disease and 5 with incomplete clinical information were excluded, and hence 74 patients were finally enrolled in this study.

This study was conducted as part of the Clinical Research Center for Dementia of South Korea-Frontotemporal Dementia (CREDOS-FTD) registry study,[14] a government-funded dementia research project conducted by dementia specialists from neurological and psychiatric clinics.[15] All patients were evaluated with comprehensive interviews, neurological examinations, and neuropsychological assessments. In brief, caregivers were interviewed in depth by neurologists and neuropsychologists. Blood tests to exclude secondary causes of dementia included a complete blood count, blood chemistry tests, thyroid function tests, vitamin B12/folate, and syphilis serology. Conventional brain MRI scans confirmed the absence of structural lesions such as brain tumors, traumatic brain injuries, hydrocephalus, or severe white matter diseases (cap or band ≥10 mm and deep white matter lesion ≥25 mm). A committee that included 5−10 dementia specialists held a quarterly meeting to review the clinical histories and brain imaging results of all cases enrolled in this study and to reach a consensus which ascertained the clinical diagnosis.

Standard protocol approvals and registration
The Institutional Review Boards at all of the participating centers approved this study. Written informed consent was obtained from all participants or their caregivers prior to conducting any study procedures.

Baseline clinical evaluation
We used the FTD Evaluation Package developed by CREDOS-FTD, which comprises a clinical evaluation form and a caregiver questionnaire form. The clinical evaluation form was designed to obtain the following information: 1) the history of cognitive decline as reported by the caregiver, 2) the results of a neurological examination, and the scores for the 3) Korean Mini-Mental State Examination (K-MMSE),[16] 4) Frontotemporal Lobar Degeneration-Clinical Dementia Rating Sum of Boxes (FTLD-CDR SB),[17] 5) Global Deterioration Scale (GDS),[18] 6) Hachinski Ischemic Scale (HIS),[19] and 7) Geriatric Depression Scale-Short Form (GDS-SF).[20]

The caregiver questionnaire form was designed to obtain the following information: 1) basic demographic data about the patient and caregiver, 2) the lifestyle and family history, 3) the past medical history including vascular risk factors, 4) Korean Dementia Screening Questionnaire (KDSQ) score,[21] 5) Barthel Activities of Daily Living (ADL) index,[22] and scores for the 6) Seoul Instrumental Activities of Daily Living (SI-ADL),[23] 7) Caregiver-Administered Neuropsychiatric Inventory (CGA-NPI),[24] and 8) Frontal Behavioral Inventory (FBI).[25]

Neurologists evaluated the baseline motor signs and symptoms of 64 patients with bvFTD using the score on the Unified Parkinson's Disease Rating Scale (UPDRS) Part III.[26]

Baseline neuropsychological assessment
All patients underwent a standardized neuropsychological test battery known as the cognitive test battery for frontotemporal dementia (FTD-Cog), which assesses the subdomains of attention, language and related functions, visuospatial function, memory, and frontal/executive function. The FTD-Cog is described in detail elsewhere.[14]

Visual rating of diffuse versus focal frontal lobe atrophy on axial MRI scans
We used an MRI visual rating scale to rate brain images in this study, which involved assessing anterior frontal lobe atrophy at the following three axial levels in T1-weighted MRI or fluid-attenuated inversion recovery MRI scans: 1) the slice just superior to the lateral ventricle on either side of the brain, 2) the slice just superior to the last view of the insular cortex on either side of the brain, and 3) the slice with the most complete view of the orbitofrontal cortex around the interpeduncular cistern (Supplementary Fig. 1 in the online-only
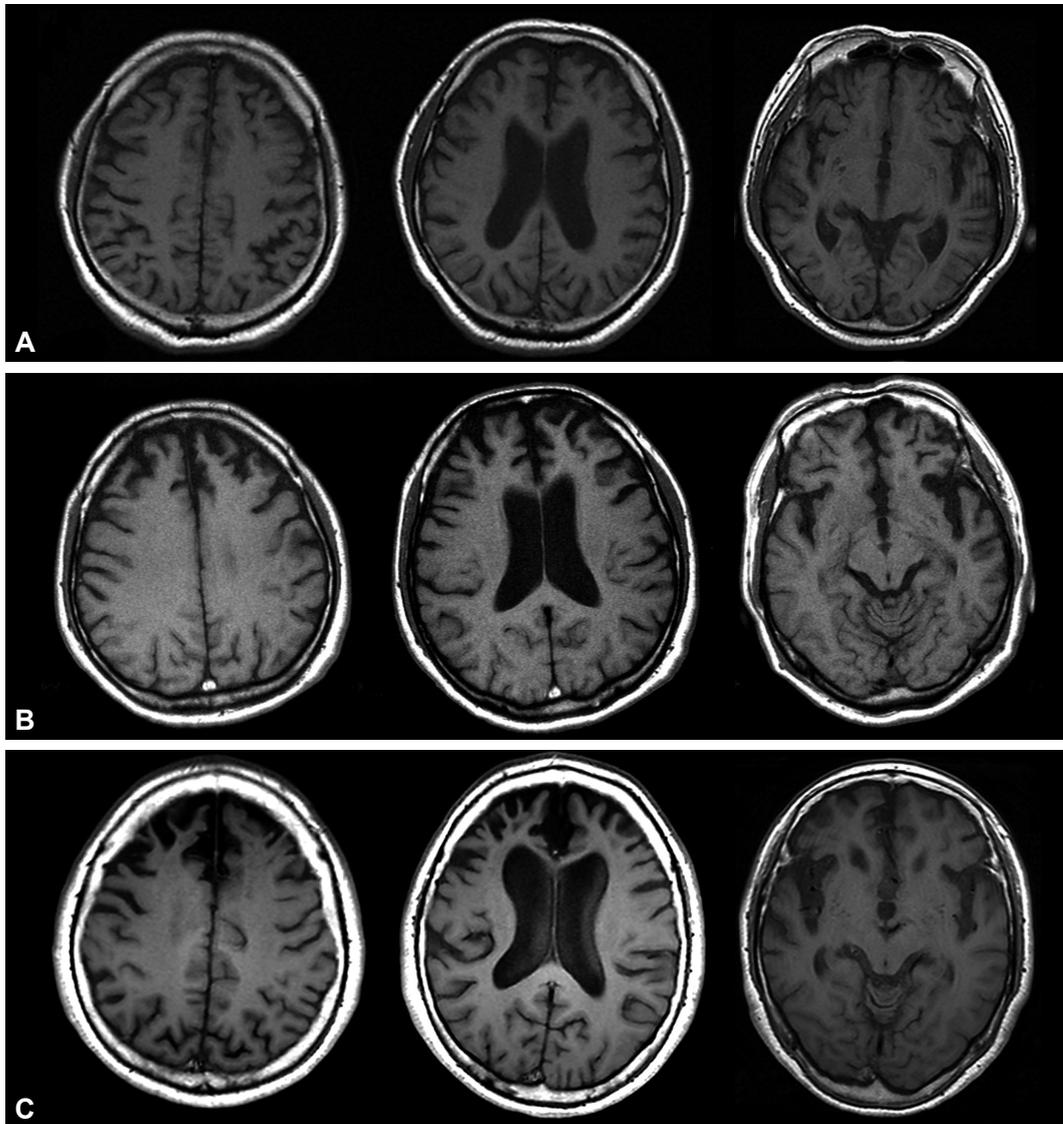
Fig. 1. Standard images for the magnetic resonance imaging (MRI) visual rating. Standard no. 1 (A), standard no. 2 (B), and standard no. 3 (C). The images in each column represent the following levels: the slice just superior to the lateral ventricle on either side of the brain (left), the slice just superior to the last view of the insular cortex on either side of the brain (middle), and the slice with the most complete view of the orbitofrontal cortex around the interpeduncular cistern (right).

Data Supplement). These three axial slices in MRI scans were referenced and modified based on previous studies.[27-29]

The ratings were performed by comparing a single selected image with three standard images (Fig. 1). The overall rating for each case was the highest (worst) atrophy rating score recorded among the three defined axial levels on the MRI scans. The lateralization of brain atrophy was recorded when the ratings for any region were not symmetric.

Ratings were based on the following scale: 0=no atrophy or diffuse atrophy (D-type), equal to standard no. 1 (Fig. 1A) and less than standard no. 2 (Fig. 1B); 1=mild-to-moderate focal atrophy (F1-type), equal to or more than standard no. 2 and less than standard no. 3; and 2=severe focal atrophy (F2-type), equal to or more than standard no. 3 (Fig. 1C). This rating process was rapid, with each case taking 2−3 min, and was based on standard clinical-quality axial MRI scans.

In this study, the scans were anonymized and their order randomized prior to rating. The ratings were performed by two neurologists who were blinded to the identity of each subject and the clinical features. The responses of the raters could have been biased if they were aware that the MRI scans they were going to rate were only from bvFTD patients, and so we included 20 MRI scans from age-matched normal controls and presented all of the MRI scans in a random order. These 20 MRI scans were from normal controls with no history of neurological or psychiatric illness, no abnormalities on neu-

rological examinations, no subjective memory complaint, and normal cognition according to the K-MMSE. Any discrepancies identified after all of the scans had been rated were resolved by consensus between the two raters.

Comparison of baseline variables between the D- and F-types

The following variables were compared between D- and F-type patients: age at symptom onset, age at diagnosis, duration of education, disease duration at diagnosis/time of MRI scan, disease duration to final follow-up, family history of dementia, Parkinson's disease, psychiatric disorders, vascular risk factors, Barthel ADL index, and scores for the K-MMSE, FTLD-CDR SB, GDS, HIS, GDS-SF, KDSQ, SIADL, CGA-NPI, FBI, UPDRS Part III, and FTD-Cog.

Comparison of motor and cognitive progression between the D- and F-types

The longitudinal progression of motor and cognitive symptoms was also compared between the two groups. A retrospective review of the full medical records was conducted by an independent neurologist who had not been involved in designing this study. The medical records were investigated for newly observed motor symptoms and disease duration. Motor symptoms were defined as significant if at least one of four cardinal signs had been observed by clinicians: rigidity, tremor, bradykinesia, or postural instability. Antipsychotics are widely applied to treat abnormal behavior symptoms in bvFTD patients, and so it is crucial to differentiate between motor symptoms with underlying neurodegenerative pathology and drug-induced parkinsonism (DIP). We therefore also investigated whether patients were taking antipsychotics as well as the causality of motor symptoms.

We were unable to apply the FTD-Cog at the follow-up to most of the participants due to their poor cooperation in these tests. Therefore, the final K-MMSE scores were used in this study to evaluate cognitive function at the follow-up.

Comparison of survival time between the D- and F-types

Survival analyses were performed in 62 of the 74 bvFTD patients, with the vital status of each confirmed using the database of the Korea Ministry of Government Administration and Home Affairs or via a telephone interview during June 2015.

Statistical analyses

Comparisons were performed across MRI visual rating subtypes and clinical data. Student's *t*-test and the chi-square test were used as appropriate to compare the demographic

and clinical characteristics of the groups. The three groups (D-, F1-, and F2-types) were compared using analysis of variance (ANOVA) with Tukey post-hoc tests. A multiple linear regression model adjusted for covariates (age at onset, sex, UPDRS Part III score at baseline, and disease duration at the time of MRI scanning) was used to evaluate the relationship between the subtypes and the disease duration without motor symptoms. Repeated-measures ANOVA with Bonferroni post-hoc test was used to compare K-MMSE scores at baseline and follow-up. In addition, we used Kaplan-Meier survival analysis grouped by MRI visual rating subtypes and with log-rank post-hoc testing. Multivariate Cox proportional-hazards regression analysis was used to identify factors that influenced survival. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. SPSS (version 20, SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

RESULTS

Inter- and intrarater agreements for the MRI visual rating scale

The intrarater reliability determined for all 94 scans was excellent, with Cohen's kappa values of 0.79 and 0.71 for raters 1 and 2, respectively. The interrater reliability analysis also showed substantial agreement, with a Cohen's kappa value of 0.82.

Based on an axial MRI visual rating scale, the 20 MRI scans from age-matched normal controls were classified into 16 D- and 4 F1-types (i.e., mild-to-moderate focal atrophy), while the 74 MRI scans from bvFTD patients were classified into 35 D- and 39 F-types. Subclassifying the 39 F-type was into two types by severity revealed 22 of the F1-type (mild-to-moderate focal atrophy) and 17 of the F2-type (severe focal atrophy). Most (*n*=57, 77.0%) of the 74 bvFTD patients had symmetric atrophy, while most (*n*=11, 64.7%) of the 17 asymmetric scans indicated left-sided atrophy.

Comparisons of baseline demographic data and dementia rating scales between the D- and F-types

The demographic and clinical data at baseline between the D- and F-types are compared in Table 1. The only significant difference between these two subtypes at baseline was in the total GDS-SF score, which was significant higher in the D-type than in the F-type [8.2±5.0 vs. 4.7±3.9 (mean±SD), *p*=0.005]. There was a tendency for the CGA-NPI total score to be higher in the D-type than in the F-type, but the difference was not statistically significant (35.8±26.0 vs. 25.6±18.9, *p*=0.068). However, comparing the subscale scores revealed that those for agitation and disinhibition were significantly higher in D-type patients than in F-type patients (Supplementary Ta-

Table 1. Baseline demographic data and dementia rating scales for the D- and F-types

	D-type (*n*=35)	F-type (*n*=39)	*p*
Sex, male (%)	60.6	51.2	0.419
Age at onset, years	63.9±10.3	62.1±10.1	0.429
Age at diagnosis, years	66.1±9.9	64.5±10.0	0.484
Education, years	9.0±5.2	11.1±5.0	0.083
Duration at diagnosis, months	31.7±24.1	34.2±18.9	0.623
Duration at time of MRI scan, months	29.2±22.4	32.2±19.3	0.538
Duration to final follow-up, months	52.7±35.3	63.0±32.8	0.197
Family history (%)			
Dementia	21.2	24.4	0.747
IPD	3.0	0.0	0.262
Psychiatric disease	6.1	2.4	0.432
Antipsychotic medication (%)	51.5	43.9	0.694
DIP causality (%)	3.0	4.9	0.689
K-MMSE score	21.1±6.2 (35)	18.6±6.1 (39)	0.092
CDR score	1.1±0.7 (35)	1.2±0.7 (39)	0.487
CDR SB score	6.5±4.5 (35)	7.1±4.2 (39)	0.537
FTLD-CDR SB score	8.6±5.2 (35)	9.4±4.8 (36)	0.509
GDS score	4.2±1.0 (35)	4.4±0.9 (39)	0.352
GDS-SF score	8.2±5.0 (27)	4.7±3.9 (30)	0.005*
KDSQ score	15.1±7.7 (32)	17.2±7.3 (37)	0.237
Barthel ADL index	17.9±2.8 (33)	17.7±3.2 (39)	0.817
SIADL score	20.1±12.7 (33)	22.0±12.0 (38)	0.517
CGA-NPI score	35.8±26.0 (33)	25.6±18.9 (38)	0.068
FBI score	34.1±12.1 (32)	32.8±12.4 (34)	0.684

Except where indicated otherwise, data are mean±SD (*n*) values.

*$p < 0.05$.

Barthel ADL index: Barthel Activities of Daily Living index, CDR: Clinical Dementia Rating, CDR SB: Clinical Dementia Rating Sum of Boxes, CGA-NPI: Caregiver-Administered Neuropsychiatric Inventory, DIP: drug-induced parkinsonism, D-type: diffuse type, F-type: focal type, FBI: Frontal Behavioral Inventory, FTLD-CDR SB: Frontotemporal Lobar Degeneration-Clinical Dementia Rating Sum of Boxes, GDS: Global Deterioration Scale, GDS-SF: Geriatric Depression Scale-Short Form, IPD: idiopathic Parkinson's disease, KDSQ: Korean Dementia Screening Questionnaire, K-MMSE: Korean Mini Mental State Examination, MRI: magnetic resonance imaging, SIADL: Seoul Instrumental Activities of Daily Living.

ble 1 in the online-only Data Supplement).

Comparisons of UPDRS Part III score and neuropsychological performance at baseline between the D- and F-types

Table 2 presents the results of comparisons of the UPDRS Part III score and neuropsychological tests between the two subtypes of bvFTD. The score for UPDRS Part III at baseline was significantly higher in the D-type (13.9±16.2) than in the F-type (6.9±10.9, *p*=0.044). D-type patients exhibited better neuropsychological performance than F-type patients, as indicated by significantly higher mean scores for the FTD-Cog total (*p*=0.024), attention (*p*=0.047), and frontal/executive function (*p*=0.006) components.

We also compared the FTD-Cog and UPDRS Part III scores among the D-, F1-, and F2-types. The mean scores for the FTD-Cog total (*p*=0.036), memory (*p*=0.016), and frontal/executive function (*p*=0.011) components differed significantly

among the three subtypes. Post-hoc analyses revealed that FTD-Cog total, memory, and frontal/executive function scores were significantly higher for the D-type than the F2-type, but not the F1-type. The UPDRS Part III scores did not differ significantly among the three subtypes (*p*=0.114).

Comparisons of motor and cognitive progression between the D- and F-types

We used the mean disease duration without motor symptoms (i.e., the period after the baseline measurements during which the patient was free of motor symptoms) to analyze the occurrence of incident motor symptoms in patients with bvFTD. Based on a retrospective review of the medical records and the UPDRS Part III scores, 23 of the 74 patients were excluded because they already had prominent motor symptoms (including 3 patients with DIP). Ten patients with absent baseline UPDRS Part III scores were also excluded, leaving 41 patients without prominent motor symptoms at baseline

Table 2. Scores for the UPDRS Part III and neuropsychological performance at baseline for the D- and F-types

	D-type	F-type	p
UPDRS Part III score	13.9±16.2 (30)	6.9±10.9 (34)	0.044*
FTD-Cog total score [312]	145.0±62.3 (35)	111.9±60.6 (38)	0.024*
FTD-Cog attention [8]	2.8±1.2 (33)	2.2±1.5 (35)	0.047*
FTD-Cog language [90]	56.2±20.8 (35)	46.6±23.6 (37)	0.073
FTD-Cog visuospatial function [37]	22.0±12.7 (34)	20.2±12.5 (36)	0.555
FTD-Cog memory [60]	17.8±9.7 (34)	13.5±9.0 (37)	0.058
FTD-Cog frontal/executive function [117]	48.9±26.2 (34)	32.2±24.2 (38)	0.006*

Data are mean±SD (*n*) values. Numbers in square brackets are the maximum possible scores.
*p<0.05.
FTD-Cog: cognitive test battery for frontotemporal dementia, UPDRS: Unified Parkinson's Disease Rating Scale.

Table 3. Motor and cognitive progression for the D- and F-types

	D-type	F-type	p
Disease duration without motor symptoms, months†	46.3±30.1 (17)	61.0±27.1 (24)	0.008*
K-MMSE score at follow-up†	18.4±7.8 (30)	11.3±8.7 (38)	0.010*

Data are mean±SD (*n*) values.
*p<0.05, †Multiple linear regressions were performed after controlling for age at onset, sex, UPDRS Part III score at baseline, and disease duration at the time of MRI scanning across the subtypes, †Repeated-measures ANOVA was performed after controlling for duration from onset to final follow-up.
K-MMSE: Korean Mini Mental State Examination, UPDRS: Unified Parkinson's Disease Rating Scale.

in this analysis: 17 with the D-type and 24 with the F-type.

The disease duration to the final follow-up was 65.1±35.8 months. Motor symptoms appeared in 9 (52.9%) of the 17 D-type patients and in 6 (25.0%) of the 24 F-type patients. The incidence rate of motor symptoms was higher in those with D-type, but the difference was not statistically significant (*p*= 0.067). Table 3 compares the disease durations without motor symptoms across the subtypes. Multiple linear regressions were performed after controlling for age at onset, sex, UPDRS Part III score at baseline, and disease duration at the time of MRI scanning across the subtypes. The MRI subtype (from D-type to F-type) was positively correlated with the increased motor-free period (β=16.423, standard error=5.826, *p*=0.008). We observed that the disease duration without motor symptoms was significantly longer for the F-type (61.0±27.1 months) than for the D-type (46.3±30.1 months).

Differences in baseline cognitive function, as evaluated using the FTD-Cog, were consistently seen in the follow-up cognitive assessments. Although the mean K-MMSE score at baseline did not differ significantly between the two subtypes (*p*=0.092) (Table 1), repeated-measures ANOVA showed that the K-MMSE score at follow-up was significantly higher in the D-type than the F-type (18.4±7.8 vs. 11.3±8.7, *p*=0.010) (Table 3) after adjusting for the duration from disease onset to the final follow-up. In addition, the K-MMSE score was significantly higher in the D-type than the F2-type (7.8±7.8, *p*<0.001), but not the F1-type (14.1±8.5, *p*=0.205).

Survival analyses

In total, 19 deaths were confirmed in survival analyses for
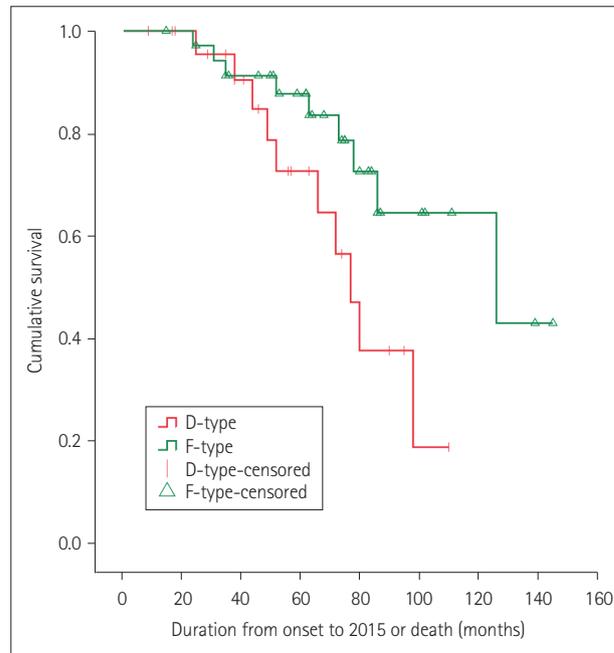
Fig. 2. Kaplan-Meier plots for groups defined by MRI visual rating subtypes. The end point is predefined as the occurrence of death (| or Δ: cases where death had not occurred by the final follow-up, *p*= 0.048 in log-rank test). D-type: diffuse type, F-type: focal type.

62 members of this cohort. The overall median survival from the onset of the first symptom was about 8.5 years. The median survival time was shorter for the D-type (6.9 years, 95% CI=5.6−8.4 years) than for the F-type (9.4 years, 95% CI= 8.0−10.8 years). Kaplan-Meier plots showed a significant difference between the D- and F-types (*p*=0.048) (Fig. 2).

We performed a multivariate Cox proportional-hazards

regression analysis to further determine the factors associated with survival. This analysis included the age at onset, sex, MRI visual rating subtypes, occurrence of motor symptoms, and the mean CDR SB, FTLD-CDR SB, and UPDRS Part III scores at baseline. The Cox regression showed that CDR SB score (HR=1.308, 95% CI=1.014−1.686, p=0.038) and UPDRS Part III score (HR=1.062, 95% CI=1.019−1.108, p=0.004) influenced the survival time after the onset of the disease, with higher scores increasing the risk of mortality.

DISCUSSION

We developed a reliable scheme for classifying 74 patients with bvFTD into the diffuse (35 patients) and focal (39 patients) types of frontal lobe atrophy using axial MRI scans. The two subtypes differed in both the prevalence of motor symptoms and survival time.

Our first major finding was that the mean UPDRS Part III score at baseline was higher (indicating greater abnormality) in the D-type than the F-type. Moreover, follow-up analyses of motor progression in patients without motor symptoms at baseline showed that the motor symptoms developed earlier in D-type than in F-type patients. Together these results suggest that extrapyramidal motor symptoms appear earlier and may progress more rapidly in D-type than in F-type patients.

Various motor symptoms are seen in bvFTD (other than motor neuron disease). These symptoms may precede, coincide, or follow abnormal behaviors, and present as rigidity, bradykinesia, abnormal posture, and (in rare cases) tremor.[30] The prevalence of motor symptoms in bvFTD patients has also varied markedly between studies, from less than 10% to 22.7%.[31-34]

Neuropathologically, bvFTD is most often one of the FTLD proteinopathies, characterized by the accumulation of abnormal protein inclusions (e.g., tau, TDP-43, and FUS) in the cytoplasm or nuclei of neuronal and glial cells. Some investigators have reported that in comparison with tau-negative bvFTD patients, tau-positive bvFTD patients are more likely to have motor symptoms suggestive of CBD or PSP, indicating that motor symptoms may predict an underlying tau pathology.[12] However, the prefrontal atrophy in patients with PSP or CBD pathology may not be so remarkable: based on previous studies, we presumed that the MRI images of PSP patients will not indicate remarkable prefrontal atrophy to parallel the frontal dysfunction on neuropsychological tests and glucose hypometabolism evident in fluorodeoxyglucose-positron emission tomography;[35] volumetric MRI studies have shown that CBD is associated with diffuse atrophy including the parasagittal and paracentral regions rather than prefrontal atrophy.[11,36] We therefore suggest that the D-type bvFTD in our study evident in axial MRI scans was related to 4R-tau-positive pathologies. On the other hand, in line with a pathology study that demonstrated a relationship between PiD and marked circumscribed prefrontal lobe atrophy,[9] our F-type patients were more likely to have either 3R-tauopathy or TDP-43 pathology. However, future studies need to further investigate this suggestion because a voxel-based morphometry study found that PiD and TDP cases exhibited fairly diffuse atrophy, whereas this was more focal in the CBD group.[37]

Our second major finding was that the survival time differed significantly between the D- and F-types. The overall median survival time in bvFTD patients was 8.5 years from disease onset, which is similar to previous reports (7.6 to 8.7 years).[31,38-41] An unexpected finding was that the cognitive function at both baseline and follow-up was better in D-type than F-type patients. However, despite this better cognitive function, the median survival time was shorter in the D-type (6.9 years) than the F-type (9.4 years). This may indicated that the appearance of motor dysfunction is more relevant than cognition to survival in bvFTD.

We therefore presume that the shorter survival in the D-type might be associated with the earlier appearance of motor symptoms compared to the F-type. Indeed, the Cox regression analyses revealed that a high UPDRS Part III score at baseline contributed to an increased risk of mortality. Another explanation for the shorter survival in D-type patients might be related to our observation that the GDS-SF and CGA-NPI total scores at baseline were higher in the D-type than the F-type. Patients with neuropsychiatric symptoms are also more likely to be treated with antipsychotics or sedatives, resulting in worse prognosis and survival.[42]

While our simple dichotomization between the D- and F-types based on frontal lobe atrophy alone is practical in clinical settings, bvFTD can be divided into several subtypes when both frontal and temporal atrophy are considered.[3] Furthermore, some bvFTD patients have right-temporal-predominant atrophy,[43] which we did not initially consider in the present study. When we reanalyzed our data using temporal atrophy as a covariate, the differences between the D- and F-types in motor symptoms and survival time disappeared. In addition, the results we obtained from the data using frontal atrophy alone were not replicated when the same analyses were performed with either temporal atrophy alone or frontotemporal atrophy combined. Details of the associated methods and results, along with representative MRI slices from all patients, are provided as supplementary data (Supplementary Methods, Supplementary Tables 2−8, and Supplementary Figs. 2 and 3 in the online-only Data Supplement).

This study was subject to several limitations. First, the clinical diagnoses of our patients were not confirmed pathologi-

cally, and so some patients diagnosed with bvFTD might have had a frontal variant of Alzheimer's disease or a mixed pathology with other etiologies.[12] Second, we did not perform follow-up evaluations of the scores for the UPDRS Part III, FTD-Cog, GDS-SF, and CGA-NPI. Finally, the causes of death were not verified in the survival analyses. Notwithstanding these limitations, this study was able to identify focal and diffuse subtypes of frontal lobe atrophy in bvFTD based on an axial MRI visual rating scale. This method was found to be rapid and reliable, and can be applied in a wide range of clinical settings. Compared with the F-type, the D-type was associated with the earlier appearance of motor symptoms, greater depressive moods and caregiver stress at baseline, and shorter survival time during the disease, even though the D-type exhibited better neuropsychological performance both at baseline and follow-up.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2017.13.3.234.

Acknowledgements

Conflicts of Interest

The authors have no financial conflicts of interest.

REFERENCES

1. Josephs KA, Hodges JR, Snowden JS, Mackenzie IR, Neumann M, Mann DM, et al. Neuropathological background of phenotypical variability in frontotemporal dementia. *Acta Neuropathol* 2011;122: 137-153.
2. Snowden JS, Bathgate D, Varma A, Blackshaw A, Gibbons ZC, Neary D. Distinct behavioural profiles in frontotemporal dementia and semantic dementia. *J Neurol Neurosurg Psychiatry* 2001;70:323-332.
3. Whitwell JL, Przybelski SA, Weigand SD, Ivnik RJ, Vemuri P, Gunter JL, et al. Distinct anatomical subtypes of the behavioural variant of frontotemporal dementia: a cluster analysis study. *Brain* 2009;132(Pt 11): 2932-2946.
4. Kim EJ, Rabinovici GD, Seeley WW, Halabi C, Shu H, Weiner MW, et al. Patterns of MRI atrophy in tau positive and ubiquitin positive frontotemporal lobar degeneration. *J Neurol Neurosurg Psychiatry* 2007;78: 1375-1378.
5. Borroni B, Benussi A, Cosseddu M, Archetti S, Padovani A. Cerebrospinal fluid tau levels predict prognosis in non-inherited frontotemporal dementia. *Neurodegener Dis* 2014;13:224-229.
6. Borroni B, Grassi M, Archetti S, Papetti A, Del Bo R, Bonvicini C, et al. Genetic background predicts poor prognosis in frontotemporal lobar degeneration. *Neurodegener Dis* 2011;8:289-295.
7. Josephs KA, Whitwell JL, Weigand SD, Senjem ML, Boeve BF, Knopman DS, et al. Predicting functional decline in behavioural variant frontotemporal dementia. *Brain* 2011;134(Pt 2):432-448.
8. Ranasinghe KG, Rankin KP, Pressman PS, Perry DC, Lobach IV, Seeley WW, et al. Distinct subtypes of behavioral variant frontotemporal dementia based on patterns of network degeneration. *JAMA Neurol*

2016;73:1078-1088.
9. Bergeron C, Morris HR, Rossor M. Pick's disease. In: Dickson DW, editor. *Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders*. Basel: ISN Neuropath Press 2003:124-131.
10. Boxer AL, Geschwind MD, Belfor N, Gorno-Tempini ML, Schauer GF, Miller BL, et al. Patterns of brain atrophy that differentiate corticobasal degeneration syndrome from progressive supranuclear palsy. *Arch Neurol* 2006;63:81-86.
11. Rankin KP, Mayo MC, Seeley WW, Lee S, Rabinovici G, Gorno-Tempini ML, et al. Behavioral variant frontotemporal dementia with corticobasal degeneration pathology: phenotypic comparison to bvFTD with Pick's disease. *J Mol Neurosci* 2011;45:594-608.
12. Forman MS, Farmer J, Johnson JK, Clark CM, Arnold SE, Coslett HB, et al. Frontotemporal dementia: clinicopathological correlations. *Ann Neurol* 2006;59:952-962.
13. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 2011;134(Pt 9):2456-2477.
14. Kim EJ, Park KW, Lee JH, Choi S, Jeong JH, Yoon SJ, et al. Clinical and neuropsychological characteristics of a nationwide hospital-based registry of frontotemporal dementia patients in Korea: a CREDOS-FTD study. *Dement Geriatr Cogn Dis Extra* 2014;4:242-251.
15. Park HK, Na DL, Han SH, Kim JY, Cheong HK, Kim SY, et al. Clinical characteristics of a nationwide hospital-based registry of mild-to-moderate Alzheimer's disease patients in Korea: a CREDOS (Clinical Research Center for Dementia of South Korea) study. *J Korean Med Sci* 2011;26:1219-1226.
16. Han C, Jo SA, Jo I, Kim E, Park MH, Kang Y. An adaptation of the Korean Mini-Mental State Examination (K-MMSE) in elderly Koreans: demographic influence and population-based norms (the AGE study). *Arch Gerontol Geriatr* 2008;47:302-310.
17. Knopman DS, Kramer JH, Boeve BF, Caselli RJ, Graff-Radford NR, Mendez MF, et al. Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. *Brain* 2008;131(Pt 11): 2957-2968.
18. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry* 1982;139:1136-1139.
19. Hachinski VC, Iliff LD, Zilhka E, Du Boulay GH, McAllister VL, Marshall J, et al. Cerebral blood flow in dementia. *Arch Neurol* 1975;32:632-637.
20. Lesher EL, Berryhill JS. Validation of the Geriatric Depression Scale-short form among inpatients. *J Clin Psychol* 1994;50:256-260.
21. Ahn HJ, Chin J, Park A, Lee BH, Suh MK, Seo SW, et al. Seoul Neuropsychological Screening Battery-Dementia version (SNSB-D): a useful tool for assessing and monitoring cognitive impairments in dementia patients. *J Korean Med Sci* 2010;25:1071-1076.
22. Sinoff G, Ore L. The Barthel Activities of Daily Living index: self-reporting versus actual performance in the old-old (> or = 75 years). *J Am Geriatr Soc* 1997;45:832-836.
23. Ku HM, Kim JH, Kwon EJ, Kim SH, Lee HS, Ko HJ, et al. A study on the reliability and validity of Seoul-Instrumental Activities of Daily Living (S-IADL). *J Korean Neuropsychiatr Assoc* 2004;43:189-199.
24. Kang SJ, Choi SH, Lee BH, Jeong Y, Hahm DS, Han IW, et al. Caregiver-Administered Neuropsychiatric Inventory (CGA-NPI). *J Geriatr Psychiatry Neurol* 2004;17:32-35.
25. Kertesz A, Nadkarni N, Davidson W, Thomas AW. The Frontal Behavioral Inventory in the differential diagnosis of frontotemporal dementia. *J Int Neuropsychol Soc* 2000;6:460-468.
26. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord* 2008;23:2129-2170.

27. Chow TW, Gao F, Links KA, Ween JE, Tang-Wai DF, Ramirez J, et al. Visual rating versus volumetry to detect frontotemporal dementia. *Dement Geriatr Cogn Disord* 2011;31:371-378.
28. Victoroff J, Mack WJ, Grafton ST, Schreiber SS, Chui HC. A method to improve interrater reliability of visual inspection of brain MRI scans in dementia. *Neurology* 1994;44:2267-2276.
29. Scheltens P, Pasquier F, Weerts JG, Barkhof F, Leys D. Qualitative assessment of cerebral atrophy on MRI: inter- and intra-observer reproducibility in dementia and normal aging. *Eur Neurol* 1997;37:95-99.
30. Pan XD, Chen XC. Clinic, neuropathology and molecular genetics of frontotemporal dementia: a mini-review. *Transl Neurodegener* 2013; 2:8.
31. Garcin B, Lillo P, Hornberger M, Piguet O, Dawson K, Nestor PJ, et al. Determinants of survival in behavioral variant frontotemporal dementia. *Neurology* 2009;73:1656-1661.
32. Piguet O, Hornberger M, Shelley BP, Kipps CM, Hodges JR. Sensitivity of current criteria for the diagnosis of behavioral variant frontotemporal dementia. *Neurology* 2009;72:732-737.
33. Seelaar H, Kamphorst W, Rosso SM, Azmani A, Masdjedi R, de Koning I, et al. Distinct genetic forms of frontotemporal dementia. *Neurology* 2008;71:1220-1226.
34. Padovani A, Agosti C, Premi E, Bellelli G, Borroni B. Extrapyramidal symptoms in frontotemporal dementia: prevalence and clinical correlations. *Neurosci Lett* 2007;422:39-42.
35. Lagarde J, Valabrègue R, Corvol JC, Pineau F, Le Ber I, Vidailhet M, et al. Are frontal cognitive and atrophy patterns different in PSP and bvFTD? A comparative neuropsychological and VBM study. *PLoS One* 2013;8:e80353.
36. Kitagaki H, Hirono N, Ishii K, Mori E. Corticobasal degeneration: evaluation of cortical atrophy by means of hemispheric surface display generated with MR images. *Radiology* 2000;216:31-38.
37. Whitwell JL, Jack CR, Parisi JE, Knopman DS, Boeve BF, Petersen RC, et al. Imaging signatures of molecular pathology in behavioral variant frontotemporal dementia. *J Mol Neurosci* 2011;45:372-378.
38. Roberson ED, Hesse JH, Rose KD, Slama H, Johnson JK, Yaffe K, et al. Frontotemporal dementia progresses to death faster than Alzheimer disease. *Neurology* 2005;65:719-725.
39. Hodges JR, Davies R, Xuereb J, Kril J, Halliday G. Survival in frontotemporal dementia. *Neurology* 2003;61:349-354.
40. Kang SJ, Cha KR, Seo SW, Kim EA, Cheong HK, Kim EJ, et al. Survival in frontotemporal lobar degeneration in a Korean population. *Alzheimer Dis Assoc Disord* 2010;24:339-342.
41. Kansal K, Mareddy M, Sloane KL, Minc AA, Rabins PV, McGready JB, et al. Survival in frontotemporal dementia phenotypes: a meta-analysis. *Dement Geriatr Cogn Disord* 2016;41:109-122.
42. Maust DT, Kim HM, Seyfried LS, Chiang C, Kavanagh J, Schneider LS, et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. *JAMA Psychiatry* 2015;72:438-445.
43. Josephs KA, Whitwell JL, Knopman DS, Boeve BF, Vemuri P, Senjem ML, et al. Two distinct subtypes of right temporal variant frontotemporal dementia. *Neurology* 2009;73:1443-1450.