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Correlations between clinical characteristics and neuroimaging in Chinese patients with subtypes of frontotemporal lobe degeneration

Zhihong Shi, MD, PhD[a,b], Shuai Liu, RN[a,b], Ying Wang, MD, MS[c], Shuling Liu, RN[a,b], Tong Han, MD, PhD[d], Li Cai, MD, PhD[c], Yuying Zhou, MD[a,b], Shuo Gao, MD, PhD[c], Yong Ji, MD, PhD[a,b,*]

Abstract

The aim of the study was to obtain an overview of the clinical and neuroimaging features of Chinese patients with subtypes of frontotemporal lobe degeneration (FTLD).

We evaluated the demographic features, clinical presentation, and lobe atrophy depicted by magnetic resonance imaging (MRI) in 133 patients with FTLD. Two positron emission tomography (PET) scans were performed at baseline: [^{11}C]Pittsburgh compound B PET to assess amyloid-β plaque load and [^{18}F]fluorodeoxyglucose (FDG) PET to assess glucose metabolism.

The behavioral variant of FTD (bvFTD) was the most common subtype (67.7%) of FTLD. The percentages of progressive nonfluent aphasia (PNFA) and semantic dementia (SD) were similar. Cerebral lobe atrophy was seen in 87.7% of the cases. The Activities of Daily Living scale, Mini-Mental State Examination, and Montreal Cognitive Assessment scores were significantly correlated with the degree of overall atrophy. The severity of abnormal behavior was correlated with right anterior and right posterior temporal atrophy scores. The overall atrophy scores and atrophy score in the left temporal region were related to cognitive outcomes and Activities of Daily Living scores. Most of the bvFTD patients presented symmetric/asymmetric hypometabolism in the bilateral temporal cortex, frontal cortex, anterior cingulate cortex, insula, and caudate nucleus. All the PNFA patients presented left dominant hypometabolism in the frontal cortex. All the SD patients presented left dominant hypometabolism in the anterior temporal cortex.

FTLD is not rare in cognitive clinics, and the ratios of subtypes in Chinese patients are similar to other ethnic groups. Overall atrophy scores, determined by MRI, were related to the severity of cognitive dysfunction and deficits in Activities of Daily Living. Patterns of hypometabolism, determined by [^{18}F]FDG PET, were more specific to subtypes of FTLD and may help provide differential diagnoses of variants of FTLD.

Abbreviations: ADL = activities of daily living scale, bvFTD = behavioral variant of frontotemporal dementia, CBD = corticobasal degeneration, CDR = Clinical Dementia Rating, FDG-PET = fluorodeoxyglucose-PET, FTLD = frontotemporal lobe degeneration, MMSE = Mini-Mental-State Examination, MND = motor neuron disease, MoCA-BJ = Montreal Cognitive Assessment – Beijing Version, NPI-Q = Neuropsychiatric Inventory Questionnaire, PIB-PET = Carbon-11-Pittsburgh compound B-positron emission tomography, PNFA = progressive non-fluent aphasia, PPA = primary progressive aphasia, PSP = progressive supranuclear palsy, SD = semantic dementia.

Keywords: [^{18}F]FDG PET, frontotemporal lobe degeneration, glucose metabolism, lobe atrophy, primary progressive aphasia

1. Introduction

Frontotemporal lobe degeneration (FTLD) is characterized by early behavioral changes or language deficits. There are 3 main subtypes of FTLD: a behavioral variant (bvFTD), progressive nonfluent aphasia (PNFA), and semantic dementia (SD).[1–4] The latter 2 variants present primary progressive aphasia (PPA). The clinical heterogeneity of FTLD is remarkable. Patients present various combinations of disinhibition, dementia, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and motor neuron disease (MND).[5,6] FTLD is a particularly important cause of dementia in patients who are younger than 65 years old, and it is as prevalent as Alzheimer's disease in this age group.[7]

Frontotemporal lobe degeneration has rarely been systematically reported in Chinese populations. Only 1 paper has reviewed the

Editor: Chaur-Jong Hu.

ZS and SL contributed equally to this study.

Authorship: YJ designed the study. ZS collected and analyzed the data and drafted the manuscript. The other authors collected and analyzed the data.

Funding: This study was supported by the Natural Science Foundation of China (no. 81571057 and 81300947), Science and Technology Project of Tianjin Municipal Health Bureau (no.2014KR10), Key Research Project of Tianjin Public Health (no. 14KG117), and Science and Technology Project of Tianjin (no.16ZXMJSY00010).

The authors have no conflicts of interest to disclose.

[a] Tianjin Key Laboratory of Cerebrovascular and Neurodegenerative Diseases, Tianjin Dementia Institute, [b] Department of Neurology, Tianjin Huanhu Hospital, [c] PET-CT Center, General Hospital of Tianjin Medical University, [d] Department of Neuroimaging, Tianjin Huanhu Hospital, Tianjin, China.

[*] Correspondence: Yong Ji, Department of Neurology, Tianjin Huanhu Hospital, Jinnan, Tianjin, China (e-mail: jiyongusa@126.com).

Medicine (2017) 96:37(e7948)

Received: 18 May 2017 / Received in final form: 3 August 2017 / Accepted: 4 August 2017

http://dx.doi.org/10.1097/MD.0000000000007948

demographic features and clinical presentations of FTLD-spectrum disorders in 49 cases in China.[8] The primary aim of the present study was to analyze the clinical characteristics, neuroimaging features, and subtypes of FTLD in outpatients at Tianjin Huanhu Hospital,Tianjin, China, from March 2011 to November 2014.

2. Methods

2.1. Patients

We conducted a retrospective cohort study. All the FTLD patients were recruited from the cognitive outpatient clinics of Tianjin Huanhu Hospital in Tianjin, China, between March 2011 and November 2014. All the recruited patients were Chinese. Full diagnostic evaluations were available in our hospital. The inclusion criteria were the following: (i) recent diagnosis of probable or possible bvFTD according to the revised diagnostic criteria for bvFTD,[4] (ii) clinical diagnosis of PPA (PNFA or SD) according to the classification of PPA and its variants,[1] clinical diagnosis of PSP according to the clinical diagnostic criteria of the National Institute of Neurological Disorders and Stroke published in 1996,[9] clinical diagnosis of CBD according to the criteria of CBS syndrome published in 2013,[10] clinical diagnosis of FTD-MND in bvFTD or PPA patients who also had upper and lower motor neuron signs on physical examination according to the revised El Escorial criteria,[11] and (iii) no diagnosis of Alzheimer's disease, vascular dementia, or severe cerebral trauma. The exclusion criteria were the following: (i) a history of drug abuse prior to developing FTLD, (ii) the presence of other factors that contribute to cognitive impairment, including metabolic diseases, inflammatory conditions, and abnormalities in syphilis serology, serum folate, and vitamin B12, and (iii) neuroimaging evidence of a large cerebral infarction or a large area of cerebral hemorrhage.

All the FTLD patients had undergone magnetic resonance imaging (MRI) or computed tomography (11 patients) within 2 weeks of diagnosis. [^{11}C]Pittsburgh compound B positron emission tomography (PIB-PET) and [^{18}F]fluorodeoxyglucose PET (FDG-PET) were performed in 30 cases whose clinical diagnosis was uncertain after review by a multidisciplinary team or for further diagnosis.

The patients who suspected AD diagnosis did not show amyloid deposit on PIB-PET scan and AD-pattern of hypometabolism on FDG-PET. The patients who have stroke histories showed lacunar infarction and without critical part involvement on MRI and the stroke has no relationship with cognitive decline. According to the NINDS-AIREN vascular dementia diagnostic criteria, vascular dementia and mixed dementia were not considered. These patients also included in the study.

This retrospective study was approved by the Research Ethics Committee of Tianjin Huanhu Hospital, and the patients or their caregivers provided written informed consent before participating in the study.

2.2. Clinical assessment instruments

The Clinical Dementia Rating (CDR) scale was used to indicate overall disability.[12] The Chinese version of the Mini-Mental State Examination (MMSE)[13] and Montreal Cognitive Assessment–Beijing version (MoCA-BJ)[14] were used to evaluate cognition. The Neuropsychiatric Inventory Questionnaire (NPI-Q) was used to assess the severity of the behavioral and psychological symptoms of dementia and associated caregiver stress.[15] The Activities of Daily Living (ADL) scale[16] was used to assess functional impairment. Scores on the ADL scale ranged from 20 to 80. Higher scores indicated greater impairment in daily life.

2.3. Magnetic resonance imaging

Magnetic resonance images were acquired within 2 weeks of the first diagnosis using a 3.0T GE scanner. T1-weighted coronal imaging was performed using a 3-dimensional spoiled-gradient recalled-echo inversion-recovery prepped sequence.

The in vivo staging method that was used to evaluate brain images involved assessment of the degree of frontal and temporal lobe atrophy at 2 defined coronal levels on MRI images.[17] The 2 coronal slices that were assessed were the same as those that were used for postmortem evaluation and consisted of the following: slice 1 (slice through the temporal pole immediately anterior to where the temporal stem connects the frontal and temporal lobes) and slice 2 (slice of lateral geniculate nuclei). An array of standard reference images was used during each evaluation to maximize consistency. The overall evaluation for each case consisted of the highest score that was recorded for each lobar slice that was assessed. We retained separate data for each lobar region. The lateralization of brain atrophy was recorded when the assessment of any region was asymmetric (i.e., the difference between hemispheres for any region was not zero). Scans from 30 control participants were added to the series of images. Controls were selected from a volunteer panel of normal individuals who were age- and sex-matched with the study patients.

The scans were anonymized, and their order was randomized prior to assessment. Imaging was performed by 2 neuroimaging clinicians who were blinded to the identity of the participants, diagnosis, and clinical features.

2.4. Positron emission tomography

Head movement was minimized using a polyurethane immobilizer that was molded around the head. The PET images were acquired on a GE Discovery LS PET/CT scanner in 3-dimensional scanning mode, yielding 35 slices (4.25 mm thickness) that covered the entire brain. PIB-PET scans were acquired during 90-min dynamic PET acquisition (34 frames: 4×15 s, 8×30 s, 9×60 s, 2×180 s, 8×300 s, 3×600 s). [^{11}C]PIB was administered into an antecubital vein as a bolus injection, with a mean dose of 370–555 MBq. The images were reconstructed to a 128×128 matrix (2.5×2.5 mm^{2}pixel size).

The FDG-PET evaluation was performed 1 hour after PIB-PET using the same scanner, scanning mode, positioning, and reconstruction matrix. The subjects received an intravenous injection of 250 MBq [^{18}F]FDG and remained in a darkened, quiet room. A 10 minutes static PET scan was performed 60 minutes after the [^{18}F]FDG injection.

2.5. Quantification of [^{11}C]PIB uptake

The uptake of [^{11}C]PIB was quantified at the voxel level using the region-to-cerebellum ratio, which is identical to the standardized uptake value ratio. This simplified quantification enables the utilization of short (30-min) image acquisition.

2.6. Automated region-of-interest analysis

Standardized regions of interest (ROIs) were defined on the MRI template image that represented brain anatomy in accordance with the Montreal Neurological Institute (MNI). We merged and

pooled subsets from the original Automated Anatomic Labeling (AAL) atlas to form the following ROIs: middle frontal gyrus, medial prefrontal cortex, lateral temporal cortex, hippocampus and parahippocampus, inferior parietal lobe, posterior cingulate cortex and precuneus, striatum, thalamus, occipital lobe, superior temporal gyrus, and supplementary motor area.

2.7. Image preprocessing

The preprocessing of the [^{11}C]PIB imaging data was performed using Statistical Parametric Mapping 8 (SPM8) software and MATLAB 2010b for Windows (Mathworks, Natick, MA). The [^{11}C]PIB integral images (data corrected for radioactive decay summed from 60 to 90 min post-injection) were created from the dynamic PET images (frames 32 to 34) and coregistered to the subject's MRI images. The MRI images were segmented into 3 classes (gray matter, white matter, and cerebrospinal fluid) in SPM8 using 16 nonlinear iterations and $7 \times 9 \times 7$ basis functions. The PET images and gray matter MRI images were then normalized using a T1-weighted MRI template that was delivered with SPM to obtain normalization parameters. The application of a 0.5 threshold to the gray matter probability map created a gray matter probability map in MNI space. The gray matter probability map was then coregistered to the AAL template, and the PET counts were extracted from the gray matter probability map and ROIs. The mean values for all the regions were calculated from the integral [^{11}C]PIB image. Target-to-cerebellum ratios were subsequently calculated for 11bilateral regions.

2.8. FDG-PET image analysis and statistical analysis

The spatial preprocessing and statistical analysis of the FDG-PET images were also performed in all the subjects using SPM8 software and MATLAB 2010b for Windows. We compared cerebral glucose metabolism between the FTLD group and the control group. FDG-PET images were converted to ANALYZE format and then normalized to the MNI standard proportional stereotaxic space. An isotropic 10 mm full-width half-maximum Gaussian spatial smoothing filter was applied to the image. All the comparisons of brain metabolism were performed on a voxel-by-voxel basis using a 2-sample *t*-test. Statistical significance was determined using an extent threshold of 50 voxels. Regions that reached an uncorrected $P < .001$ were considered statistically significant.

2.9. Statistical analysis

Descriptive statistics, including frequencies of categorical variables and medians or means and standard deviations of continuous variables, were determined for the baseline variables. The continuous demographic and clinical variables of the patients were analyzed using analysis of variance or the Kruskal–Wallis test, which was used for data with a non-normal distribution and heterogeneity of variance. The χ^2 test was used for categorical variables. Spearman rank correlation was used to evaluate ordinal datasets. Values of $P < .05$ were considered statistically significant. All the data were analyzed using SPSS20.0 software for Windows.

3. Results

3.1. Patient demographics

A total of 133 consecutivepatients with FTLD (72 females and 61 males) were evaluated in this study. During the same time period, 632 patients were diagnosed with Alzheimer's disease. Demographic characteristics are shown in Table 1.The distribution of patients according to age was the following: 35 (26.3%) were younger than 60 years old, 28 (21.1%) were 60 to 64 years old, 28 (21.1%) were 65 to 69 years old, 18 (13.5%) were 70 to 74 old, and 24 (18.0%) were ≥ 75 years old. Eighty (60.1%) of the patients were < 65 years old at the age of onset. The mean MMSE score upon initial presentation was 17.2 ± 7.7.

Table 1

Demographic and clinical characteristics of total study cohort of patients with frontotemporal lobe degeneration (FTLD) and patients stratified according to subtypes: bvFTD, PNFA, and SD.

Number	Total, N = 133	bvFTD, n = 90	PNFA, n = 15	SD, n = 16	*P*
Female, %	72 (54.1)	50 (55.6)	6 (40.0)	9 (56.3)	.490
Age at evaluation, median, y	65.4	66.0	62.0	63.0	.106
Age at onset, media, y	63.0	63.9	60.0	60.5	.136
Illness Duration, years	2.4 ± 1.1	2.6 ± 1.1	2.0 ± 1.1	2.5 ± 1.2	.220
Educational level, years	9.1 ± 4.1	9.2 ± 4.1	7.5 ± 4.1	10.5 ± 4.1	.277
BMI, kg/m^2	23.4 ± 3.6	23.4 ± 3.8	23.1 ± 3.5	22.4 ± 3.0	.666
Family history	36 (27.1)	22 (24.4)	4 (26.7)	4 (25.0)	.279
Medical comorbidities					
Hypertension	32 (24.1)	25 (27.8)	3 (20)	2 (12.5)	.451
Diabetes	11 (8.3)	7 (7.8)	1 (6.7)	3 (18.8)	.289
Heart disease	14 (10.5)	12 (13.3)	0	2 (12.5)	.326
Stroke	10 (7.5)	8 (8.9)	1 (6.7)	1 (6.3)	.935
Smoking	31 (23.3)	21 (23.3)	4 (26.7)	4 (25.0)	.923
Alcohol drinker	19 (14.3)	13 (14.4)	2 (13.3)	3 (18.8)	.834
MMSE	17.2 ± 7.7	17.0 ± 7.5	16.6 ± 8.6	17.3 ± 7.9	.969
MoCA	10.9 ± 7.0	11.0 ± 7.0	9.7 ± 7.1	10.1 ± 5.4	.803
ADL	32.7 ± 13.2	34.1 ± 13.5	26.6 ± 8.8	27.0 ± 9.2	.026
CDT	2.0 ± 1.5	2.0 ± 1.6	1.9 ± 1.6	2.0 ± 1.5	.969
CDR	1.2 ± 0.7	1.3 ± 0.7	1.2 ± 0.7	1.1 ± 0.6	.613

Data are represented as mean ± SD, median, or n (%), *P*-values (comparing bvFTD, PNFA, and SD groups) based on analysis of variance and Kruskal–Wallis tests for continuous variables and chi-square tests for categorical variables.

ADL = activities of daily living, BMI = body mass index, bvFTD = behavioral variant FTD, CDT = Clock drawing test, MMSE = Mini-Mental State Examination, MoCA = Montreal Cognitive Assessment, PNFA = progressive nonfluent aphasia, SD = semantic dementia.

Table 2

Summary of characteristics of cognitive and behavior changes in patients with variants of frontotemporal lobe degeneration (FTLD).

	bvFTD n=90	PNFA n=15	SD n=16	PSP n=6	CBD n=2	FTD-MND n=4
Memory loss	33	12	13	4	1	2
Disinhibition	58	6	12	0	1	2
Apathy/inertia	34	6	10	2	2	1
Loss of empathy	30	1	4	2	0	1
Obsess/compul	23	4	4	1	0	0
Dietary changes	24	1	2	1	0	1
Hallucinations	14	0	2	1	0	1
Language disturbance	28	15	16	1	0	2

bvFTD = behavioral variant FTD, CBD = corticobasal degeneration, FTD-MND = frontotemporal dementia-motor neuron disease, FTLD = frontotemporal lobe degeneration, Obsess/compul = obsessions/compulsions, PNFA = progressive nonfluent aphasia, PSP = progressive supranuclear palsy, SD = semantic dementia.

3.2. Clinical characteristics of the patients stratified by FTLD subtype

According to the clinical diagnosis, bvFTD was the most common diagnostic subtype, accounting for 67.7% of the133 patient diagnoses (n=90), followed by SD (n=16, 12.0%), and PNFA (n=15, 11.3%). The demographic and clinical characteristics of the patients according to the main FTLD subtype are shown in Table 1. No significant differences in the baseline characteristics of the patients were found between the bvFTD, PFNA, and SD subtypes. The ADL scores in patients with bvFTD were significantly higher than the scores in patients with PFNA and SD.

The main signs of the patients with bvFTD at diagnosis were disinhibition (n=58), apathy/inertia (n=34), memory loss (n=33), loss of empathy (n=30), obsessions/compulsions (n=23), and dietary changes (n=24). Language impairment was present in 28 bvFTD patients. Most of the PNFA (n=12) and SD (n=13) patients presented memory loss. Most of the SD patients presented disinhibition (n=12) and apathy/inertia (n=10; Table 2).

3.3. Atrophy scores across FTLD subtypes

The MRI scans of the control participants were scored as 0 or 1 for the 3 lobar regions, thus defining the normal range. Some degree of cerebral atrophy was found (scores of 2–4) in 87.7% of the overall patient sample (100% of SD patients, 78.6% of PNFA patients, and 89.0% of bvFTD patients; Table 3).

The relative scoring of frontal and temporal lobe atrophy in individual cases differed across subtypes. In bvFTD patients, frontal lobe atrophy scores were often higher than temporal lobe atrophy scores (42.7%).The opposite was true in 78.6% of the SD patients, with significantly higher scores for anterior temporal lobe atrophy ($P<.001$). Half of the PNFA patients had equal scores for frontal and anterior temporal lobe atrophy, and the other half had greater frontal lobe atrophy, which was significantly different from SD patients ($P<.001$) but not from bvFTD patients.

Most of the aphasic patients had left-dominant atrophy (57.1% of PNFA patients, 78.6% of SD patients). Symmetrical scans were found in 41.5% of the bvFTD patients, which was significantly different from PNFA and SD patients ($P<.001$).

3.4. Glucose metabolism determined by FDG-PET according to FTLD subtype

Thirty patients underwent PIB-PET and FDG-PET upon initial diagnosis. All the patients were PIB-negative based on visual

Table 3

Summary of lobe atrophy on magnetic resonance images of patients with main subtypes of frontotemporal lobe degeneration (FTLD).

	Total, n=122	bvFTD, n=82	PNFA, n=14	SD, n=14	*P*
Overall atrophy level					.321
0	1 (0.8)	0	0	0	
1	14 (11.5)	9 (11.0)	3 (21.4)	0	
2	57 (46.7)	38 (46.3)	7 (50.0)	5 (35.7)	
3	40 (32.8)	29 (35.4)	3 (21.4)	6 (42.9)	
4	10 (8.2)	6 (7.3)	1 (7.1)	3 (21.4)	
Left and right atrophy levels					.001
Left worse	42 (34.4)	21 (25.6)	8 (57.1)	11 (78.6)	
Right worse	34 (27.9)	27 (32.9)	2 (14.3)	3 (21.4)	
Uniform	46 (37.7)	34 (41.5)	4 (28.6)	0	
Frontal and anterior temporal					.000
Frontal worse	51 (41.8)	35 (42.7)	7 (50.0)	3 (21.4)	
Anterior temporal worse	34 (27.9)	21 (25.6)	0	11 (78.6)	
Uniform	37 (30.3)	26 (31.7)	7 (50.0)	0	
Anterior and posterior temporal					.248
Anterior temporal worse	34 (27.9)	26 (31.7)	2 (14.3)	4 (28.6)	
Posterior temporal worse	27 (22.1)	17 (20.7)	1 (7.1)	4 (28.6)	
Uniform	61 (50.0)	39 (47.6)	11 (78.6)	6 (42.8)	

Data are represented as n (%), *P*-values (comparing bvFTD, PNFA, and SD groups) based on chi-square tests for categorical variables; Worse: means higher score and therefore increased atrophy; Uniform: means equal levels of atrophy.

bvFTD = behavioral variant FTD, CBD = corticobasal degeneration, FTLD = frontotemporal lobe degeneration, PNFA = progressive nonfluent aphasia, SD = semantic dementia.

Table 4

Summary of hypometabolism on FDG-PET of patients with main subtypes of frontotemporal lobe degeneration (FTLD).

	Total, n = 30	bvFTD, n = 12	PNFA, n = 4	SD, n = 4	CBD, N = 2	PSP, N = 6	FTD-MND, N = 2
Left and right							
Left dominant	9	0	4	4	0	1	0
Right dominant	4	1	0	0	2	1	0
Symmetric	17	11	0	0	0	4	2
Frontal and anterior temporal							
Frontal worse	14	6	4	0		2	2
Anterior temporal worse	10	3	0	4	2	1	0
Uniform	6	3	0	0	0	3	0

bvFTD = behavioral variant FTD, CBD = corticobasal degeneration, FDG-PET = fluorodeoxyglucose-PET, FTD-MND = frontotemporal dementia-motor neuron disease, FTLD = frontotemporal lobe degeneration, PNFA = progressive nonfluent aphasia, PSP = progressive supranuclear palsy, SD = semantic dementia.

assessment. Of the 12 bvFTD patients who underwent PET, 11 presented symmetric/asymmetric hypometabolism in the bilateral temporal cortex, frontal cortex, anterior cingulate cortex, insula, caudate nucleus, and bilateral (or unilateral) medial thalamic regions, and one presented hypometabolism in the right temporal-parietal cortex, posterior cingulate cortex, and bilateral caudate nucleus. Four PNFA patients presented hypometabolism in the left dominant frontal cortex or frontal-temporal cortex, anterior cingulate cortex, insula, caudate nucleus, and medial thalamic regions. All 4 SD patients presented left dominant hypometabolism in the temporal cortex. Two patients also presented hypometabolism in the left parietal cortex. One patient presented hypometabolism in the left occipital cortex. Six PSP patients presented hypometabolism in the frontal cortex, temporal cortex, thalamus, insula, caudate nucleus, and midbrain. Four patients presented symmetric hypometabolism in the frontal and temporal lobe. One patient presented left dominant hypometabolism in the frontal and temporal lobe. One patient presented hypometabolism only in the right frontal and temporal lobe. Two CBD patients presented hypometabolism in the right frontal, temporal, parietal cortex, caudate nucleus, and insula. Two FTD-MND patients presented hypometabolism in the bilateral frontal lobe, anterior cingulate cortex, caudate nucleus, and temporal lobe (Table 4, Fig. 1).

3.5. Relationship between atrophy scores and clinical measures

The MMSE and MoCA scores of all the patients were correlated with overall atrophy scores (Spearman's $\rho = -0.200$, $P = .027$, and $\rho = -0.204$, $P = .025$, respectively). The CDR scores were also significantly correlated with atrophy scores (Spearman's $\rho = 0.227$, $P = .012$).

The summed severity of behavioral scores that were extracted from the NPI-Q did not correlate with overall atrophy scores but were correlated with right anterior and right posterior temporal lobe atrophy scores (Spearman's $\rho = 0.308$, $P = .013$, and $\rho = 0.270$, $P = .031$, respectively) in all the patients.

3.6. Follow-up evaluations

A total of 53 patients were followed for longer than 1 year. MMSE testing at 12 months of follow-up found that 15 patients had stable cognitive status, 38 patients presented cognitive decline (i.e., MMSE scores decreased ≥2 points relative to baseline), and 23 patients presented significant decline (i.e., MMSE scores decreased ≥4 points relative to baseline). A positive correlation was found between the decrease in MMSE scores and baseline left anterior and left posterior temporal lobe atrophy scores (Spearman's $\rho = 0.322$, $P = .026$, and $\rho = 0.403$, $P = .005$, respectively) in all the patients who were followed up at 12 months. The ADL scores in 41 patients at the 12-month follow-up significantly increased (i.e., worsened) relative to baseline. A positive correlation was found between the increase in ADL scores relative to baseline and overall atrophy (Spearman's $\rho = 0.407$, $P = .007$), left anterior temporal lobe atrophy (Spearman's $\rho = 0.343$, $P = .024$), and left posterior temporal lobe atrophy (Spearman's $\rho = 0.321$, $P = .036$) in all the patients who were followed up at 12 months.

4. Discussion

Dementia research in Asia has focused on Alzheimer's disease and vascular dementia, whereas FTLD has not been extensively studied in Asian and Pacific Islander populations. To our knowledge, this is the first study that summarized the demographic, clinical, and neuroimaging characteristics of a large series of Chinese patients with FTLD. The female-to-male ratio was 1.3:1. Of the patients, 24.6% were ≤ 60 years old, and 44.2% were 60 to 69 years old. The percentages of bvFTD, PNFA, and SD patients were 67.7%, 11.3%, and 12.0%, respectively. A positive family history was found in 27.1% of our patients, which is somewhat lower than in other studies.

In the present study, 44.2% of the FTLD patients were 60 to 69 years old. A study of a population in The Netherlands[18] found that 12.7% of FTLD cases were < 50 years old, and 22% were >65 years old. The prevalence of FTLD was the highest in patients who were 60 to 69 years old. A study of a population in Great Britain[19] focused on young-onset dementias (i.e., dementia in individuals who were <65 years old) and found that 12% of FTLD cases were <50 years old.

bvFTD accounted for nearly 60% of the FTLD cases. The language variants were less common. The largest clinical study that analyzed data from 2 centers in the United States and 1 center in Germany (n = 353) found that 57% of the cases were behavioral variants, and 43% were language variants.[20] In the present study, 67.7% of the FTLD patients were diagnosed with bvFTD, 23% were diagnosed with PPA, and 6% were diagnosed with other variants, including PSP, FTD-MND, and CBD.

Among our patients, changes in behavior and language deficits were the main clinical characteristics, but memory deficits were also a main complaint that concomitantly occurred with behavioral changes and language deficits. However, these patients did not present amyloid deposition on PIB-PET, but they were still diagnosed with FTLD. Patients with FTLD

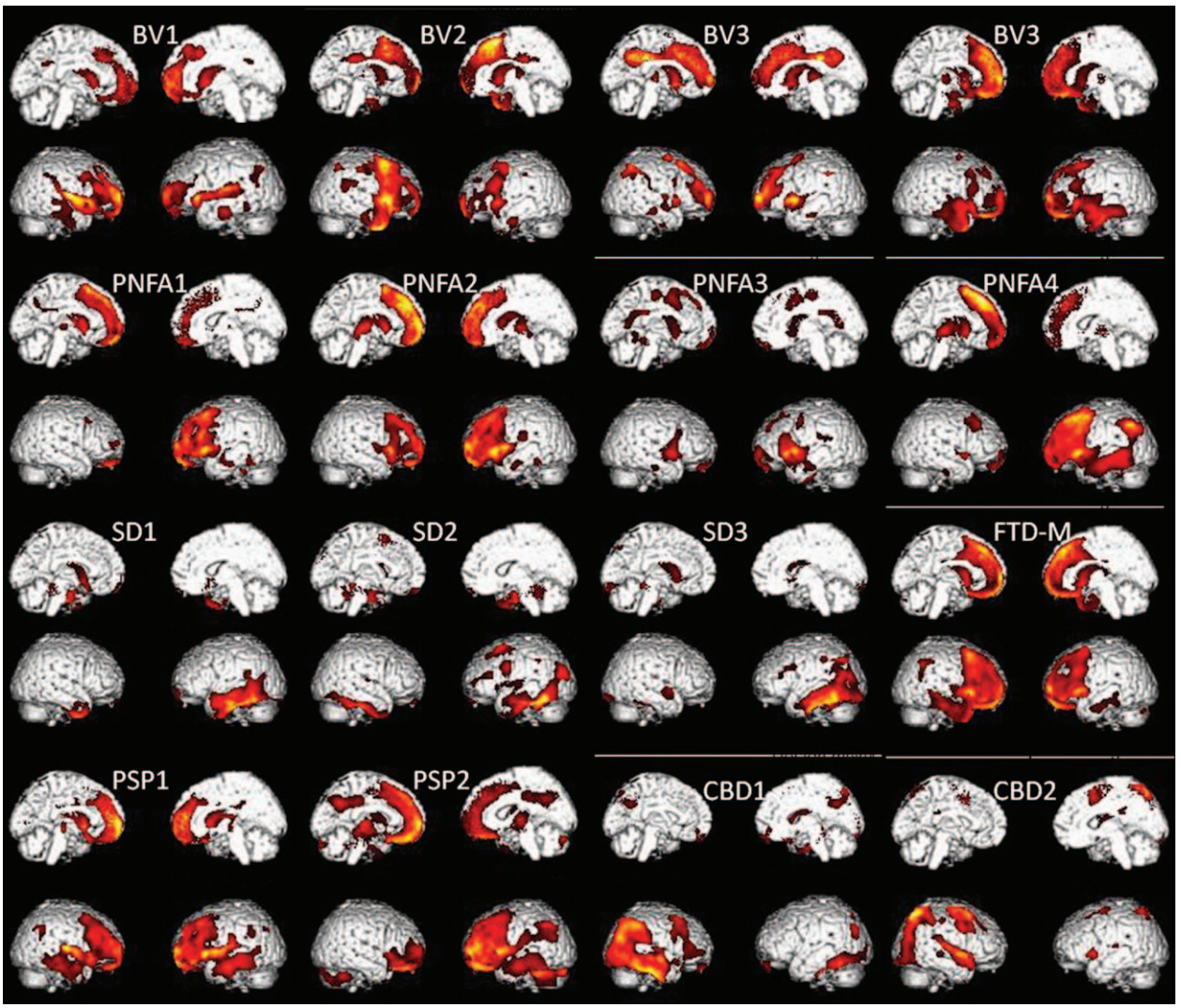

Figure 1. Hypometabolic regions in individual patients with subtypes of FTLD compared with the healthy control group (uncorrected $P < .001$). BV = bvFTD, FTD-M = FTD-MND.

commonly complain of memory loss and memory underperformance,[21,22] and many patients who had pathology that confirmed FTLD also met the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for possible or probable Alzheimer's disease.[23] A recent review of clinicopathological correlations in a cohort of 61 patients with pathologically proven FTLD reported that 5 patients (8%) presented memory loss as their primary complaint.[24] Graham et al[25] found that 8 of 71 cases (11%) had early and severe memory impairment as the major presenting clinical feature, but the pathological diagnosis was FTLD. In the present study, most of the PPA patients (80.6%) and 36.7% of the bvFTD patients had memory loss at presentation. These results indicate that memory loss is also a major manifestation of different subtypes of FTLD.

We used a visual scale to semiquantitatively assess brain atrophy in 122 clinically defined cases of FTLD. The majority of the patients (87.7%) had evidence of frontal and/or temporal atrophy, which is consistent with the fact that our patients presented for neurological evaluation at a relatively advanced stage. The profiles of lobar atrophy were consistent with the criteria of consensus documents.[1,3] Frontal atrophy scores were generally higher in bvFTD cases, and temporal atrophy scores were higher in SD cases. These findings reflect the respective synonyms of "frontal" and "temporal" variants. Lobar atrophy in frontal regions in PNFA cases in the present study was worse than atrophy in anterior temporal regions. In SD cases, in contrast, anterior temporal regions had worse atrophy compared with frontal regions.

On FDG-PET, the bvFTD cases presented glucose hypometabolism in the bilateral frontal cortex, temporal cortex, anterior cingulate cortex, insula, caudate nucleus, and medial thalamic regions. These patterns of hypometabolism have been reported in previous studies.[26–28] Jeong et al[26] reported hypometabolism in frontal and anterior temporal areas, the cingulate gyri, the uncus, the insula, and subcortical areas, including the basal ganglia and medial thalamic regions in FTLD cases. They also found that the hemispheric asymmetry of hypometabolism (more frequently lateralized to the left) was common in patients with FTLD. In our cases, patterns of symmetric or right-dominant hypometabolism were common.

All the PNFA cases presented patterns of hypometabolism that were similar to bvFTD, but they had left dominant hypometabolism in the frontal cortex, which is different from the symmetric or right dominant hypometabolism that was found in bvFTD cases. The SD cases presented left temporal dominant glucose hypometabolism, with or without parietal hypometabolism. The PNFA and SD patients presented different patterns of hypometabolism, which are more obvious than structural MRI scans. These findings are consistent with the functional and structural imaging results of previous studies.[29–34]

The CBD cases presented hypometabolism in the right frontal, temporal, and parietal cortices and caudate nucleus. The PSP cases presented symmetric or asymmetric hypometabolism in the frontal cortex, temporal cortex, thalamus, insula, caudate nucleus, and midbrain. These patterns of hypometabolism were very specific to CBD and PSP patients, which may facilitate a differential diagnosis of CBD and PSP as previously reported.[35–37]

Of the clinical measures of symptom severity, scores on the CDR scale, MMSE, and MoCA were correlated with overall atrophy scores of the entire cohort. Notably, the severity of behavioral scores on the NPI-Q did not correlate with overall atrophy scores but did correlate with right temporal atrophy scores of the entire cohort. This indicates that the right temporal lobe was closely related to behavioral changes.

The relationship between focal atrophy and disease progression is still unclear. In the present study, the 12-month follow-up of some patients showed that cognitive decline was correlated with left anterior and left posterior temporal lobe atrophy scores. Additionally, ADL scores were positively correlated with overall atrophy scores and with left anterior and left posterior temporal lobe atrophy. Larger studies are needed to confirm that left temporal atrophy is a prognostic indicator of rapid cognitive decline.

The present study has limitations. First, our patients were selected based on their clinical features. Histopathological confirmation was unavailable for any of our patients. The clinical features of some of our patients may have also been manifestations of other dementias (e.g., Alzheimer's diseaseor Lewy body dementia). PIB-PET was performed to exclude amyloid deposition, but we could not identify whether Alzheimer's disease and FTLD coexisted in our cases. Second, we did not compare the imaging findings of our FTLD patients with those of patients with other neurodegenerative diseases. Therefore, unknown is whether our atrophy assessment scale is able to differentiate FTLD variants from neurodegenerative diseases (e.g., Alzheimer's disease) that are diagnosed clinically. Third, the small sample of patients who underwent FDG-PET prevented further investigation of possible correlations between glucose metabolism, clinical characteristics, and disease progression. Prospective validation in a wider cohort is in progress.

This retrospective study analyzed the clinical characteristics, MRI features, and disease subtypes of 133 Chinese patients with FTLD. bvFTD was the most common subtype (67.7% of patients). The SD and PNFA subtypes had similar rates of occurrence. Cerebral atrophy was seen in 87.7% of the cases. Scores on the CDR scale, MMSE, and MoCA were correlated with the degree of overall atrophy. The severity of behavioral scores on the NPI-Q was correlated with right temporal lobe atrophy scores. The patterns of hypometabolism, revealed by FDG-PET, were specific to FTLD subtypes, which may help with differential diagnoses of FTLD variants.

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