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Frontotemporal Dementia: Pathology of Gait?

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Abstract: The main diagnostic criteria of the behavioural variant of frontotemporal degeneration (bvFTD) include neurobehavioral and dysexecutive syndromes, but not specific gait characteristics although strong relationship between gait and prefrontal functions are increasingly recognized. Accordingly, we tested the hypothesis that patients with bvFTD would have more gait changes than older healthy controls and demented patients with Alzheimer's disease (AD). Sixty subjects were included in the study: 19 with bvFTD, 19 with AD and 22 healthy controls. Mean values and coefficients of variation (CV) of stride time while just walking (i.e., single tasking) and while walking with backward counting (i.e., dual tasking) were measured using the SMTEC®-footswitch system. Stride time, mean value, and CV were significantly increased in both patient groups compared with healthy controls during single task or walking alone ($P < 0.001$) and during dual tasking ($P < 0.001$). After adjusting for age, Mini-mental examination, psychoactive drugs, gender, and history of previous fall, only the patients with bvFTD group was associated with an increase of CV of stride time during single walking ($P < 0.001$) and dual tasking ($P < 0.001$). These data suggest that gait instability during single and dual tasking could represent a supportive argument for bvFTD. In clinical practice, such a diagnosis should be at least considered in any demented patient with gait instability. © 2010 Movement Disorder Society

Key words: frontotemporal dementia; gait disorders; Alzheimer's disease; executive function; motor control

INTRODUCTION

Gait was considered as an automated motor activity independent of cognition, but recent studies underscored that gait and higher-level cognitive function seem to be closely related in healthy older adults and demented subjects.[1–4] Gait changes are frequently observed in the latter[2] and predict further development of dementia in nondemented subjects, either of any type[3] or specifically of non-Alzheimer's disease type.[4]

Dual-task paradigms, measuring the ability to accurately allocate attention between two tasks performed simultaneously (two cognitive tasks or gait and cognitive one) are increasingly recognized as a marker of executive dysfunction.[1,5] Stride time variability was significantly associated with executive function in nondemented older adults.[6] Patients with Alzheimer's disease (AD) or mixed dementia presenting with impaired executive functions exhibited an increase in stride-to-stride variability during single and dual tasking.[7,8] From a methodological perspective, we also showed in a group of demented patients with executive dysfunctions that the best dual-task parameter was the coefficient of variation (CV) of stride time.[5] Previous data

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strongly suggest that altered executive functions play a crucial role in gait disorders and specifically in dual-task related gait changes. We thus decided to shift the focus of interest from AD, where the dysexecutive syndrome is associated with other cognitive dysfunctions that may also contribute to gait changes, to patients presenting with long-lasting isolated prefrontal syndrome such as patients with a behavioral variant of frontotemporal degeneration (bvFTD).

Patients with bvFTD, a subgroup of frontotemporal lobar degeneration, present a neurobehavioural syndrome usually associated with a dysexecutive syndrome. Clinical diagnosis criteria for bvFTD include an insidious onset, a gradual progression, early decline in social interpersonal conduct, early impairments in regulation of personal conduct, an emotional blunting and loss of insight.[9] Apart from primitive reflexes that are minor criteria, other motor impairments, and particularly gait disorders, are not required for establishing the diagnosis, despite that it seems to exist some overlap between bvFTD and other pathologies involving motor system (such as amyotrophic lateral sclerosis). In a comparative study, a subgroup of patients in an early stage of bvFTD showed more involuntary trunk movements than AD.[10] Although substantial data suggest that executive functions are involved in gait control in older adults, there is no data regarding gait analysis in bvFTD or comparing gait parameters of bvFTD and AD.

The goal of this study was to compare gait variability between bvFTD, AD, and healthy controls and to describe the specificity of gait disorders in bvFTD using normal gait and gait during dual-tasking. On the basis of the strong relationship between executive functions and gait variability, we hypothesized that bvFTD patients could have higher gait variability than patients with AD and healthy controls.

METHODS

Subjects

The subjects' population involved 19 bvFTD, 19 AD, and 22 controls. They were evaluated at Pitié-Salpêtrière Hospital in Paris and at Angers University Hospital (France). They underwent a full neurological examination, a clinical interview including the use of psychoactive drugs (benzodiazepines, antidepressants and neuroleptics) and the number of drugs taken per day, behavioral evaluations, neuropsychological testing, brain MRI or CT-Scan imagery and 99mTc-ECD brain SPECT perfusion (for bvFTD and patients with AD).

The diagnosis of bvFTD was based on the revised Lund and Manchester criteria.[9,11] Additional criteria for the diagnosis were a hypoperfusion strictly restricted to the frontal lobes on the SPECT and absence of significant limb apraxia, visuospatial deficit or cued recall impairment (after successful encoding) in episodic memory tasks in the neuropsychological evaluation. Patients with both bvFTD and motor neuron disease or with familial history of both pathologies were also excluded to avoid a motor deficit that would potentially interfere with gait. AD subjects met NINCDS-ADRDA criteria for probable Alzheimer's disease.[12] Control subjects had no neurological complaints, normal neurological and neuropsychological examinations. In all groups, exclusion criteria included extrapyramidal rigidity of the upper limbs with a score above 2, based on item 22 of the UPDRS-motor score; acute medical illness in the past months; neurological and psychiatric diseases except dementia; severe orthopaedic or rheumatologic condition affecting normal walking, as well as use of walking aids. All subjects gave informed consent according to the ethical standards set forth in the declaration of Helsinki (1983). For severely demented individuals who could not give informed consent, consent was provided by the closest family member or caregiver. The local ethics committee approved the project.

Neuropsychological Evaluation

The patients were evaluated with a standardized neuropsychological battery including the Mini Mental State Examination of Folstein (MMSE),[13] the MATTIS Dementia Rating Scale,[14] the Frontal Assessment Battery (FAB),[15] and the Free and Cued Recall Test.[16]

Gait Recordings

Gait analysis included the following tasks that were randomized to minimize practice effect: walking only; backward counting down by one from 50 to 1 while walking, and backward counting while sitting. Before testing, a trained evaluator gave standardized verbal instructions on the test procedure along with a visual demonstration of the walking test. For dual-tasking, the subjects were asked to walk and to count backwards at the best of their capacity. To get the participants used to gait testing, they undertook one walking trial. The figures enumerated while walking were the only one taken into account. The cognitive performance was counted as the sum of correct answers. The time needed to achieve the 10 meters walking distance and the number of enumerated figures during this time were recorded using SMTEC® system (SMTEC®, Sport & Medical Technologies SA, Nyon Switzerland), which

TABLE 1. *Clinical characteristics of the control group, the Alzheimer's disease group (AD) and the behavioral variant of frontotemporal degeneration group (bvFTD)*

	Control (n = 22)	AD (n = 19)	bvFTD (n = 19)	*P*-value
Clinical measures				
Sex (female), n (%)	14.0 (63.6)	13.0 (68.4)	9.0 (47.4)	0.454
Age (mean ± SD)*	71.0 ± 0.5	79.3 ± 8.4	66.8 ± 9.7	<0.001
Age at onset (mean ± SD)*		76.3 ± 8.9	62.1 ± 9.6	<0.001
Level of education (>16 years), n (%)*	3.0 (13.6)	1.0 (5.3)	11.0 (57.9)	0.001
Number of comorbidities ≥ 3, n (%)	8.0 (36.4)	1.0 (5.3)	5.0 (27.8)	0.099
Previous fall, n (%)	5.0 (22.7)	13.0 (68.4)	5.0 (26.3)	0.006
UPDRS score (1/4), n (%)	3.0 (13.6)	7.0 (36.8)	5.0 (26.3)	0.253
MMSE				
Value (median ± IQR)	29 ± 1	19 ± 7	26 ± 6	<0.001
Score ≤ 24 (%)	0 (0)	15.0 (78.9)	8.0 (42.1)	<0.001
Treatments				
≥4 drugs per day, n (%)	3.0 (13.6)	5.0 (26.3)	2.0 (10.5)	0.003
Psychoactive drugs, n (%)	4.0 (18.2)	12.0 (63.2)	10.0 (52.6)	0.009
Neuroleptics, n (%)	0 (0)	1.0 (5.3)	5.0 (26.3)	0.006
Antidepressants, n (%)	0 (0)	3.0 (15.8)	9.0 (47.4)	<0.001
Benzodiazepins, n (%)	4.0 (18.2)	12.0 (63.2)	4.0 (21.1)	0.006
Anticholinesterase inhibitors, n (%)	0 (0)	2.0 (10.5)	3.0 (15.8)	0.147
Cognitive performance				
Number of figures WBC (mean ± SD)	19.1 ± 3.9	19.2 ± 6.4	17.5 ± 5.5	0.552
Number of figures BC (mean ± SD)	21.6 ± 4.1	18.3 ± 6.3	21.4 ± 8.5	0.168

P-Value: Comparison among three groups based on Fisher's exact test or Kruskal-Wallis ANOVA as appropriate; SD: Standard deviation; UPDRS: based on item 22 of the Unified Parkinson's Disease Scale motor score; MMSE: Mini Mental State Examination; WBC: walking while backward counting; BC: backward counting.

*$P < 0.01$ between AD and bvFTD.

consists of two footswitches providing a continuous measurement of temporal step parameters.[17] This system is a pair of innersoles fitted inside the subject's shoes. Each innersole contains two independent footswitches placed at the heel and the toe, which are linked to a portable data logger worn at the waist. The time was calculated using the first contact which is defined by the activation of the heel sensors and the last contact which corresponds to the time when the toe sensor goes off of walkway. Afterwards, we asked the patients to sit and enumerate as many numbers as possible within the same period of time. Each subject completed one trial for each walking condition. The subjects wore their own footwear. Mean values and coefficients of variation (CV)(CV = (standard deviation / mean) × 100) of step time, stride time, swing time, and stance time for all walking conditions were determined during steady-state walking using the SMTEC® system.[17] For the comparison between bvFTD, AD and healthy controls, we focused on backward counting as dual-tasking.

Statistics

Subjects' characteristics were described using means and standard deviations or frequencies and percentages, as appropriate. The normality of the parameters' distribution was checked with skewness and kurtosis tests before and after applying usual transformations to normalize non-Gaussian variables. First, comparisons between groups were performed using the independent samples *t*-test, the Kruskal-Wallis test, one-way analysis of variance (ANOVA) or Chi-square test, as appropriate. Second, univariate (model 1), bivariate model adjusted on gait speed (model 2) and multivariate (model 3) linear regressions were used to examine the association between CV of stride time (independent variable) and type of dementia (AD versus bvFTD; dependent variable) while taking the subjects' baseline characteristics into account. *P*-values less than 0.05 were considered statistically significant. All statistics were performed using the Stata Statistical Software, version 10.1.

RESULTS

Demographic and Clinical Characteristics

Demographic and clinical characteristics are summarized in Table 1. Specifically, the bvFTD patient group was significantly younger than the AD patient group ($P < 0.001$) but not than the control group ($P = 0.382$). The bvFTD and the AD patient groups

TABLE 2. *Mean value and standard deviation of stride time parameters under single and dual-task conditions*

Stride time (mean ± SD)	Control (n = 22)	AD (n = 19)	bvFTD (n = 19)	*P*-value
Single task (walking alone)				
Mean Value	1.036 ± 0.100	1.184 ± 0.132*	1.128 ± 0.107**	<0.001
CV	0.017 ± 0.005	0.031 ± 0.012*	0.077 ± 0.082**	<0.001
Dual task (walking and backward counting)				
Mean Value	1.143 ± 0.175	1.355 ± 0.209*	1.314 ± 0.201**	<0.001
CV	0.027 ± 0.009	0.06 ± 0.031*	0.083 ± 0.062**	<0.001

AD, Alzheimer's disease group; bvFTD, behavioural variant of frontotemporal degeneration group; *P*-Value, Comparison among three groups based on Kruskal-Wallis ANOVA as appropriate; CV, coefficient of variation.

*$P < 0.01$ between control and AD.

**$P < 0.01$ between control and bvFTD.

differed in terms of level of education ($P < 0.001$), age ($P < 0.001$) and age at onset of disease ($P < 0.001$), but not for MMSE. The three groups were significantly different regarding the number of previous falls ($P = 0.006$; AD > bvFTD and healthy controls), the number of drugs taken per day ($P = 0.003$), and specifically for psychoactive drugs including neuroleptics ($P = 0.006$; bvFTD > AD and controls), antidepressants ($P < 0.001$; bvFTD > AD and healthy controls), benzodiazepines ($P = 0.006$; AD > healthy controls and bvFTD).

Gait Data

For usual walking, the mean value of stride time was significantly different between the three groups ($P < 0.001$), but there was no difference between the bvFTD and the patients with AD groups ($P = 0.13$). The CV of stride time significantly differed between groups ($P < 0.001$), with a highest variability for the bvFTD patient group (7.7 %) but without significant difference between both demented groups ($P = 0.12$) (Table 2). The mean value of gait speed significantly differed between the three groups ($P = 0.009$), with a slowest gait speed for the AD group (110.6 ± 9.9 cm/s) and a fastest one for the control group (118.5 ± 11.7 cm/s).

While dual-tasking, the mean value of stride time was significant between groups ($P < 0.001$), but not between both demented patients groups ($P = 0.272$). For the CV of stride time, there was a highest value in the patients with bvFTD group (8.3 %) with a significant difference between the three groups ($P < 0.001$) (Table 3). For the mean gait speed, we also observed a significant difference between the three groups ($P = 0.002$), with a slowest speed for the patients with bvFTD group (88.9 ± 10.0 cm/s) and a fastest one for the control group (102.3 ± 12.4 cm/s) (Table 3).

Simple regression showed that patients presenting with AD ($P < 0.001$), bvFTD ($P < 0.001$), taking psychoactive drugs ($P = 0.006$) and poor score at MMSE ($P = 0.026$) were associated with an increase of the CV of stride time during single task (Table 4). In the bivariate regression model adjusted on gait speed, we found the same significant associations. After adjusting for all variables, only bvFTD remains associated with the increase of CV of stride time ($P < 0.001$). Under

TABLE 3. *Mean value of gait speed under single and dual-task conditions*

Gait speed (mean ± SD)	Control (n = 22)	AD (n = 19)	bvFTD (n = 19)	*P*-value
Single task (walking alone)				
Mean gait speed (cm/s)	118.5 ± 11.7	110.6 ± 9.9*	111.8 ± 9.0**	0.009
Dual task (walking and backward counting)				
Mean gait speed (cm/s)	102.3 ± 12.4	89.4 ± 22.5	88.9 ± 10.0**	0.002

AD, Alzheimer's disease group; bvFTD, behavioural variant of frontotemporal degeneration group; *P*-value, Comparison among three groups based on Kruskal-Wallis ANOVA as appropriate; CV, coefficient of variation.

*$P < 0.01$ between control and AD.

**$P < 0.01$ between control and bvFTD.

TABLE 4. *Univariate (model 1), bivariate adjusted on gait speed (model 2) and multivariate linear regressions (model 3) showing the cross-sectional association between CV of stride time during single task (independent variable) and type of dementia (dependant variable) adjusted for subjects' baseline characteristics*

	Model 1 (nonadjusted)			Model 2 (bivariate model adjusted on gait speed)			Model 3 (adjusted on all subjects' baseline characteristics)		
	Coef β	95% CI	*P*	Coef β	95% CI	*P*	Coef β	95% CI	*P*
Control	1.00	–			–		1.00	–	
bvFTD	−3.05	[−4.07;−2.03]	<0.001	−3.21	[−4.26;−2.15]	<0.001	−3.18	[−4.47;−1.90]	<0.001
AD	−2.01	[−3.03;−0.1]	<0.001	−2.19	[−3.26;−1.12]	<0.001	−1.31	[−3.19;0.56]	0.165
Psychoactive drugs	−1.45	[−2.46;−0.43]	0.006	−1.48	[−2.50;−0.46]	0.005	−0.42	[−1.43;0.58]	0.401
MMSE	0.10	[0.01;0.2]	0.026	0.10	[0.01;0.20]	0.031	0.02	[−0.10;0.14]	0.722
Age	−0.01	[−0.07;0.05]	0.721	−0.01	[−0.07;0.05]	0.773	−0.04	[−0.11;0.03]	0.248
Sex	0.08	[−1.02;1.18]	0.885	0.02	[−1.11;1.14]	0.976	0.38	[−0.62;1.37]	0.451
Previous fall	−0.88	[−1.96;0.2]	0.108	−0.85	[−1.95;0.24]	0.125	−0.33	[−1.42;0.75]	0.543
Gait speed	0.01	[−0.03;0.06]	0.575		–		−0.03	[−0.07;0.02]	0.269

Coef β, coefficient β; CI, Confidence interval; $P < 0.05$ was considered statistically significant; bvFTD, behavioral variant of frontotemporal degeneration group; AD, Alzheimer's disease group; MMSE, Mini Mental State Examination.

dual-task, simple regression showed that patients presenting with AD ($P < 0.001$), bvFTD ($P < 0.001$), poor score at the MMSE ($P = 0.003$), gait speed ($P = 0.030$) and taking psychoactive drugs ($P = 0.002$) were associated with an increase in the CV of stride time during dual task (Table 5). In the bivariate regression model adjusted on gait speed, bvFTD ($P < 0.001$), AD ($P = 0.001$) and taking psychoactive drugs ($P = 0.018$) were associated with an increase of CV during dual task. After adjusting for all variables, only bvFTD remains associated with the CV of stride time during dual task ($P < 0.001$).

Performance of Cognitive Task

The AD, the bvFTD, and the healthy control subjects enumerated, respectively, 19.2 ± 6.4, 17.5 ± 5.5, and 19.1 ± 3.9 figures while walking. There was no significant difference between groups ($P = 0.552$). While sitting, they enumerated respectively 18.3 ± 6.3, 21.4 ± 8.5, and 21.6 ± 4.1 without significant difference between groups ($P = 0.168$) (Table 1).

DISCUSSION

We tested the hypothesis that patients with bvFTD would have higher stride-to-stride variability while dual-tasking, than patients with AD and healthy older controls. Stride time, mean value and CV, were significantly increased in both patient groups comparing to healthy controls during single task or walking alone and during dual tasking. After adjusting for confounding variables including gait speed, only the patients with bvFTD group was associated with CV of stride time during single walking task and during dual-tasking. There was no significant difference between the

TABLE 5. *Univariate (model 1), bivariate adjusted on gait speed (model 2) and multivariate linear regressions (model 3) showing the cross-sectional association between CV of stride time during dual task (independent variable) and type of dementia (dependant variable) adjusted for subjects' baseline characteristics*

	Model 1 (nonadjusted)			Model 2 (bivariate model adjusted on gait speed)			Model 3 (adjusted on all subjects' baseline characteristics)		
	Coef β	95% CI	*P*	Coef β	95% CI	*P*	Coef β	95% CI	*P*
Control	1.00	–			–		1.00	–	
bvFTD	−1.87	[−2.75;−1.00]	<0.001	−2.95	[−4.05;−1.86]	<0.001	−2.92	[−4.17;−1.66]	<0.001
AD	−1.88	[−2.75;−1.00]	<0.001	−1.91	[−3.00;−0.83]	0.001	−1.03	[−2.87;0.79]	0.261
Psychoactive drugs	−1.27	[−2.07;−0.47]	0.002	−1.24	[−2.27;−0.22]	0.018	−0.59	[−1.56;0.40]	0.237
MMSE	0.11	[0.04;0.18]	0.003	0.08	[−0.01;0.18]	0.079	0.02	[−0.09;0.14]	0.693
Age	−0.02	[−0.07;0.03]	0.472	−0.01	[−0.06;0.06]	0.916	−0.04	[−0.11;0.03]	0.274
Sex	−0.14	[−1.01;0.74]	0.754	0.01	[−1.06;1.06]	0.998	0.24	[−0.74;1.22]	0.619
Previous fall	−0.56	[−1.44;0.31]	0.200	−0.61	[−1.70;0.48]	0.269	−0.32	[−1.43;0.79]	0.567
Gait speed	0.03	[0.01;0.06]	0.030		–		0.01	[−0.03;0.03]	0.970

Coef β, coefficient β; CI, Confidence interval; $P < 0.05$ was considered statistically significant; bvFTD, behavioural variant of frontotemporal degeneration group; AD, Alzheimer's disease group; MMSE, Mini Mental State Examination.

three groups in terms of cognitive performance, in the single task and in the dual task. These findings show, for the first time, that bvFTD is associated with a gait disorder that can be evidenced by using specific and accurate markers of gait processing.

Gait and Frontal Lobe

Our findings suggest that the patients with bvFTD present increase gait variability even in a single walking task in comparison with healthy controls and patients with AD (Table 4). In 1960, gait apraxia was related to frontal lobe dysfunction in general[18] or more specifically to its medial prefrontal regions.[19] In this line of ideas, a few case studies reported the observation of patients with isolated medial frontal lobe lesions associated with gait apraxia.[20,21] Frontotemporal dementia was associated with bilateral atrophy of the frontal and anterior temporal lobes more than 30 years ago, and recently confirmed using voxel-based morphometry.[22] In comparison with AD, the pattern of atrophy in frontotemporal lobar degeneration is anatomically distinct including a more severe atrophy in medial prefrontal cortex.[23] Thus, the gait variability shown in bvFTD in our study could be related to a specific disturbance of the medial prefrontal cortex.

Dual Tasking and Frontal Lobe

Dual tasking challenges one's ability to allocate attentional ressources toward two tasks performed in parallel. The increased CV under dual tasking confirmed that gait is influenced by the concurrent performance of a cognitive task and, therefore should not be considered as an automatic function. In our study, both patients groups presented worse performance during walking and backward counting than the control group (Table 2). Furthermore, the stride time variability during dual tasking was only associated with the patients with bvFTD group (Table 5). Similar changes in dual-tasking were reported in various conditions associated with executive dysfunction and affecting basal ganglia, frontal regions or their reciprocal connections (frontosubcortical circuits) such as in Parkinson's disease,[24] Huntington's disease,[25] AD[7] mood disorders,[26] and attention deficit hyperactivity disorder.[27] Functional neuroimaging studies have shown that the performance of dual-tasking was associated with activation located in the anterior cingulate cortex and the prefrontal regions[28,29]—a group of brain regions that are essential for executive functions. Since dysexecutive deficits are encountered in AD and bvFTD, and predominantly in the latter,[30] it is not surprising that both patients groups were impaired in dual-tasking, particularly the patients with bvFTD group in our study.

Stride Time Variability and Executive Functions

Among many gait parameters, the one that is the most closely associated with executive functions is stride time variability[5–7] considered as the neural control implied in the maintenance of a steady walking rhythm. This parameter was significantly associated in single and dual tasks after adjusting for all variables only with bvFTD (Tables 4 and 5). This association can be related to the dysexecutive syndrome present in patients with bvFTD, such as difficulty planning and executing motor sequences. Similar results were described in elderly fallers,[31] suggesting that gait stability requires a low variability. Freezing of gait, that presents an extraordinary way of gait variability, was associated with executive dysfunction in patients with high level of gait disorders[32] and with Parkinson's disease.[33]

Study Limitations

A main limitation of our study was that our demented patients did not have autopsy-confirmed diagnoses. Our small sample size also necessitates caution. In addition, the bvFTD patient group presented a higher level of education than the patients with AD group (Tables 1). However, to the best of our knowledge, there are no published data showing a relationship between gait and level of education. Finally, the SMTEC® system provides only the measurement of temporal step parameters contrary to electronic walkway, but this drawback is compensated by its possible use in ambulatory settings; it could be interesting to evaluate in a future study the differences of the spatial features of gait between bvFTD, AD and healthy older subjects.

CONCLUSION

Patients with bvFTD had an increase variability of stride time in comparison with AD patients and healthy controls. Stride time variability during single and dual-tasking could represent a supportive argument for the diagnosis of bvFTD and we would advocate gait assessment in the work-up of dementia. Although the gait variables described in this study require the use of footswitches or others instruments, simple gait assessment during single and dual-tasking can be easily appreciated at bedside. As gait disorders can be evidenced in bvFTD, in demented patients with gait instability, the diagnosis of bvFTD should be considered.

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