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Comparative Study of Subcortical Atrophy in Patients with Frontotemporal Dementia and Dementia with Extrapyramidal Signs

Leonardo Caixeta[1,*], Renata Teles Vieira[2], Flávia Paes[4], Mauro Giovanni Carta[3], Antonio Egidio Nardi[4], Oscar Arias-Carrión[5], Nuno B. F. Rocha[6], Henning Budde[7] and Sergio Machado[4,8]

[1]*Neuropsychiatry, School of Medicine, Federal University of Goiás (UFG). Dementia Outpatient Unit, Hospital das Clínicas-UFG, Brazil;* [2]*Behavioral and Cognitive Neurology Unit, Hospital das Clínicas, Federal University of Goiás, Goiânia (GO), Brazil;* [3]*Department of Public Health, Clinic and Molecular Medicine - University of Cagliari, Italy;* [4]*Laboratory of Panic and Respiration, Institute of Psychiatry of Federal University of Rio de Janeiro (IPUB/UFRJ), Brazil; National Institute for Translational Medicine (INCT-TM), Brazil;* [5]*Unidad de Trastornos del Movimiento y Sueño (TMS), Hospital General Dr. Manuel Gea Gonzalez, Secretaria de Salud, México, DF, México;* [6]*Polytechnic Institute of Porto, School of Allied Health Sciences, Portugal;* [7]*Medical School Hamburg, Faculty of Human Sciences, Department of Pedagogy, Germany; Reykjavik University, School of Science and Engineering, Department of Sport Science, Iceland;* [8]*Physical Activity Neuroscience, Physical Activity Postgraduate Program, Salgado de Oliveira University (UNIVERSO), Niterói, RJ, Brazil*

Abstract: *Objectives*: To investigate the severity of subcortical atrophy in frontotemporal dementia (FTD) without extrapyramidal symptoms (EPS) and dementia with EPS. In addition, we aim to verify if there is correlation between demographic and clinical characteristics and subcortical atrophy in the groups. *Methodology*: The sample was composed of 21 patients with dementia and EPS as well as 19 patients with FTD without EPS. A linear assessment was conducted in order to identify the degree of subcortical atrophy (i.e., bifrontal index - BFI) using MRI. Moreover, the Mini-Mental State Examination (MMSE), Pfeffer Functional Activities Questionnaire (FAQ) and the Clinical Dementia Rating (CDR) were used to investigate clinical aspects. *Results*: It was verified that patients with dementia and EPS was older than the patients with FTD (p=0.01). The severity of cognitive deficits was associated with BFI, as well as the dementia severity in the EPS group. *Conclusion*: FTD group presented mean BFI scores above the cutoff for normal elderly population, indicating the presence of subcortical atrophy in this group. Mean BFI was higher (although not statistically significant) in FTD group than in dementia with EPS, which can suggest at least that subcortical pathology in FTD may be as important as in the dementia with EPS group. Subcortical atrophy is a good biological marker for cognitive deterioration in FTD and in dementia with EPS.

Keywords: Bifrontal index, extrapyramidal signs, frontotemporal dementia, structural neuroimaging, subcortical atrophy.

INTRODUCTION

Brain atrophy is observed in almost all types of dementia. It is caused by a loss of brain volume, indirectly observed by an enlargement of brain sulci and ventricles [1]. Studies using magnetic resonance imaging (MRI) with linear and volumetric measures to examine brain atrophy have been proposed to track this decline [2-5].

Bifrontal index (BFI) and ventricle-brain ratio, indirect measures of subcortical atrophy, have been used by many researchers to investigate structural brain lesions in dementia patients. Both volumetric and linear measurements are more reliable than those made postmortem because ventricles tend to shrink after death [2-5, 27, 28]. One of the earliest changes seen in brain atrophy is the dilatation of the frontal horns of the lateral ventricle, BFI is one of the most consistent and practical linear measurement, when compared with other indexes, to estimate early brain atrophy [23]. The rate of cerebral atrophy has been studied as a biomarker for some neurodegenerative disorders, however its clinical importance and its relationship with extrapyramidal signs (EPS) has not been examined widely [6].

Frontotemporal Dementia (FTD) is the most common form of dementia with the onset before 60 years of age. Its typical symptoms include behavioral disorders like affective symptoms, and language disorders [7]. The clinical syndrome of FTD overlaps with frontal-subcortical circuit syndromes [8, 9]. Also several studies on different approaches propose a subcortical and deep cortical involvement in FTD, but few researches have widely evaluated the related subcortical changes [8-12]. Many authors have studied the pattern of atrophy in FTD patients, but have not investigated subcortical atrophy specifically [13-17].

The aim of this research was to compare the degree of subcortical cerebral atrophy in FTD and in other dementias with EPS. In addition, we associated age, duration and stage of disease, educational level, activities of daily living (ADL)

*Address correspondence to this author at the Instituto da Memória, Avenida Cristo Rei, 626, setor Jaó, Goiânia (GO), Brazil. CEP 74674290; Tel: + 55-62-32047223; E-mail: leonardocaixeta1@gmail.com

and cognition with brain subcortical atrophy in both groups, in order to test the influence of EPS in brain subcortical atrophy.

METHODOLOGY

Sample

Forty patients diagnosed with dementia in the Hospital das Clínicas at Federal University of Goiás School of Medicine (FM-UFG) participated of the study. The sample was composed of 21 patients with dementia and EPS as well as 19 patients with FTD, aged 33 to 99 (mean: 68.35; SD: ±13.09), schooling ranging from 1 to 20 years (mean: 8.06; SD: ± 6.52) and duration of disease (mean: 3.84; SD: ±3.44). The group of patients with dementia with EPS was composed of individuals with vascular dementia (VD), Alzheimer's disease (AD), corticobasal degeneration, Parkinson disease dementia (PDD), Lewy Body dementia (LBD).

Patients were diagnosed by an experienced neuropsychiatrist based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), patient's history, neuropsychiatric exam, routine laboratory screening, neuroimaging exams (MRI and SPECT in all sample) and neuropsychological assessment [18]. The diagnosis of dementia types and of FTD was based on Neary *et al.* criteria [19]. EPS were assessed using part III of Unified Parkinson Disease Rating Scale (UPDRS-III). Specific EPS can be diagnosed when any of the following conditions are present: (1) two or more UPDRS ratings (bradykinesia, rigidity or tremor) =1, or (2) one UPDRS rating (≥ 2 or 3) the UPDRS rest tremor ≥1 [20].

Patients in use of neuroleptic agents or antiparkinson medication, with hydrocephalus, tumor or other structural lesions, history of traumatic brain injury and FTD with parkinsonism (for instance FTDP-17) were excluded.

All participants or main caregivers were made aware of the entire experimental protocol and signed a consent form before participating in this study. This study was approved by the Ethics Committee at Federal University of Goiás.

Instruments

Bifrontal Index - BFI MRI was performed on a 1.5 – T MRI unit with a quadrature head coil, analyzing T1-weighted sequences. From the axial slice of MRI, the BFI was measured on a plane parallel to the temporal lobe plane at the level of the maximal width between the tips of the frontal horns of the lateral ventricles, and defined as the ratio of this measure to the diameter of the inner skull table at the same level multiplied by 100 to express as a percentage [4, 5, 21, 22]. Linear measures as BFI are used to establish the presence of ventricular enlargement and subcortical atrophy [37].

Clinical Dementia Rating (CDR) - The severity of dementia was determined by total sum of the CDR. The CDR assesses six domains of cognition, i.e., memory, orientation, judgment and problem solving, community affairs and personal care. Based on six scores, a global CDR score is assigned: CDR 0 is no dementia, CDR 0.5 is very mild dementia, CDR 1 is mild dementia, CDR 2 is moderate dementia, and CDR 3 is severe dementia [24].

Mini-Mental State Examination (MMSE) - General cognitive functioning was tested using MMSE [25]. The MMSE examines orientation, attention, calculation, immediate and short-term memory, language and praxis. Reliability and construct validity of the test are considered good [25]. All patients completed the MMSE at baseline.

Pfeffer Functional Activities Questionnaire (FAQ) – It was completed by caregivers of dementia patients. It assesses functional capacity, and is composed of ten questions of activities of daily living (ADL) [26]. All patients were evaluated with BFI, CDR, MMSE and FAQ; therefore duration of dementia and education level were also assessed and served as input for the survival analysis. The neurological examination was performed during the same period as clinical imaging. The BFI was compared in both groups and for all analyzed variables.

Statistical Analysis

The Mann-Whitney test (U) was performed to compare mean rates of variable between the two patient groups. The analyzed variables were: age, duration of dementia, MMSE scores, Functional Scale of Pfeffer's scores, level of education in years, CDR and BFI rate. We established the confidence interval as 95% for the statistical tests. Spearman' s rank correlation coefficient (Rho) was used to obtain the correlation p and to verify the correlations between mean rates of brain atrophy (measured by BFI) and all other variables. The Spearman Coefficient is the non-parametric alternative when the data is not Gaussian and linear. We conducted all statistical analysis using the SPSS 20.0 software for Windows.

RESULTS

The clinical features and the results from BFI for FTD and dementia with EPS groups can be observed in Table **1**. There were no significant differences between groups regarding the BFI. Also, no significant statistical difference was found between FTD and dementia with EPS groups with respect to all the demographics features and clinical variables analyzed (Mann- Whitney test), except that the patients with dementia and EPS that were statistically older than the patients with FTD (p=0.01). Table **2** shows a correlation among IBF with age, duration of dementia, cognitive function, ADL, education level and score the severity of dementia, using the coefficient of Spearman. It was observed both in the first group (patients with FTD without EPS) as the second group (Dementia and EPS) that the IBF was related with cognitive function checked through the MMSE ($p \leq 0.05$). With regard to the patients with dementia and EPS, we can see that besides the cognitive function also the severity of dementia interrelated with the BFI ($p \leq 0.05$). From the data analysis we find that age, activities of daily life and educational level were not correlated to BFI in the groups ($p \leq 0.05$).

DISCUSSION

Our DFT group presented mean IBF scores above the cutoff for normal elderly population [32], indicating the presence of subcortical atrophy in this group. Besides that, mean IBF was higher (although not statistically significant)

Table 1. Comparison of subcortical atrophy, demographic factors and duration of symptoms in patients with FTD and Dementia with EPS.

	Frontotemporal Dementia (n=19) M± SD	CI 95%	Dementia and EPS (n=21) M±SD	CI 95%	U	Z	p*
Age, y	63.36±12.32	57.43|-|69.43	72.86±12.36	67.23|-|78.48	104.5	-2.57	0.01**
Dementia duration, y	5.02±4.33	2.94|-|7.11	2.76±1.42	1.89|-|3.64	145.0	-1.48	0.137†
MMSE Score	11.95±9.53	7.35|-| 16.54	14.95±7.43	11.57|-|18.34	152.0	-1.291	0.197†
FAQ	21.63±10.58	16.53|-|26.73	20.29±9.61	15.91|-|24.66	179.0	-0.574	0.56†
Education, y	7.76±5.87	4.93|-|10.59	8.33±7.20	5.06|-|11.61	187.5	-0.320	0.744 †
BFI	35.40±5.36	32.2|-|37.99	34.22±4.80	32.04|-|36.41	166.5	-0.894	0.371†

*Significance *on Mann-Whitney* Test (*U*); ** Statistically significant difference p< 0.05; † No significant between group difference p>0.05; MMSE, Mini-Mental State Examination; BFI, Bifrontal Index; EPSs, Extrapyramidal Signs; FAQ, Pfeffer-Functional Activities Questionnaire; M, Mean; SD, Standard Deviation; CI, Confidence interval; Z, standard normal deviate.

Table 2. Correlation of BFI with demographic factors, disease severity and the duration of symptoms at two groups.

	Frontotemporal Dementia		Dementia and EPS	
Age, y	-0.404	0.086†	0.325	0.150†
Dementia duration, y	-0.063	0.796†	0.0331	0.800†
MMSE score	-0.564	0.012*	-0.540	0.011*
FAQ	0.265	0.273†	0.320	0.157†
Education, y	0.164	0.502†	0.167	0.468†
CDR	0.163	0.505†	0.573	0.007*

*Denotes *p* value of < 0.05† Differences of modalities not significant (*p*>0.05); MMSE, indicates Mini-mental State Examination; CDR, Clinical Dementia Rating; BFI, Bifrontal Index; EPSs, Extrapyramidal Signs; FAQ, Pfeffer-Functional Activities Questionnaire.

in FTD group than in dementia with EPS, which may suggest at least that subcortical pathology in FTD may be as important as in the dementia with EPS group. To our knowledge, this is the first study to compare subcortical atrophy between FTD and dementia with EPS. It is also the first using BFI to address this comparison.

Subcortical atrophy, as measured by structural MRI may indicate a subcortical contribution to the progression of FTD. We found a consistent pathology of subcortical structure complementing the typical frontotemporal cortical atrophy. Subcortical grey matter atrophy may contribute as significantly to symptoms of FTD as cortical atrophy [9]. The subcortical and deep cortical structures may provide important clues on the clinical expression of this disorder, including also cognitive and behavioral abnormalities, given the growing consensus on the involvement of the basal ganglia in non-motor functions such as language, executive functions, memory, and learning [6].

BFI appears unsatisfactory for the differential diagnosis between FTD and dementia with EPS. Vieira and Caixeta [6] also found BFI unsatisfactory for the differential diagnosis between FTD and AD. Chaves *et al.* [32] also found that BFI from Alzheimer and vascular patients were not significantly different. In accordance to other previous studies, a biomarker of a single region seems unsatisfactory to discriminative between FTD and other dementias [5, 13, 14]. This may reflect the different patterns of regional brain atrophy in each dementia subtype.

When we compared the means of the variables analyzed between the FTD group and dementia with EPS group, there was a statistically significant difference only in age (it was higher in the EPS group). This finding was consistent with published reports in the literature when comparing FTD with other old-age dementia groups, since FTD is predominantly an early-onset dementia form [29-31]. An unexpected finding was that even with these younger subjects, FTD patients have IBF scores similar to older patients from the EPS group with dementia.

The mean of the BFI in the FTD group was 35.4%, while in the dementia plus EPS group was 34.2%. Chaves *et al.* [32] found a BFI mean by 35.8% for demented patients without EPS. Frisoni *et al.* [5] obtained a mean of 33.3% from 14 FTD patients.

A significant negative correlation was found between BFI scores and cognitive performance in MMSE in both groups. A previous study conducted by our group found a

very similar association studying comparatively FTD and AD [6]. Several other studies have reported that subcortical structures are associated with deficits of language and cognitive functions [8, 33, 34]. Soderlund *et al.* [35] noted that subcortical brain atrophy estimated by ventricular expansion was also associated with higher cognitive deficits in FTD. Based on these collected data, it can be assumed that subcortical atrophy is a good biological marker of cognitive deterioration in FTD and dementia with EPS.

Only in the group with dementia and EPS the BFI had a significant positive correlation with the overall severity of dementia (CDR), suggesting that rates of subcortical cerebral atrophy may provide a reasonable mark to the severity of some dementia forms, but this could not be extended to FTD. On the other side, Whitwell *et al.* [14] found that CDR scores were also significantly associated with the ventricular volume in FTD, suggesting that rates of cerebral atrophy provide excellent markers of disease progression in this dementia form. The contradictory results in this topic deserve additional investigation and may be sometimes related to the use of different brain measures among studies.

Subcortical atrophy was not correlated with age in none groups of our sample. On the contrary, Mackenzie & Feldman [36] showed that patients with extrapyramidal features and dementia have higher degeneration of subcortical structures and these abnormalities are more common with advanced age.

It is important to mention that a linear measure of subcortical atrophy (BFI) is probably unsatisfactory for the differential diagnosis between FTD and other dementias, but may be useful in differentiating non-demented FTD phenocopies (for example, bipolar disorder and apathetic depression) from "real" FTD patients. Although we commonly find some degree of frontal atrophy in bipolar disorder [38] and depression [39] which may present as a 'frontal type pseudodementia', it was never reported the presence of subcortical atrophy in these functional psychiatric disorders; therefore BFI may represent an useful tool in order to differentiate 'frontal type pseudodementia' from FTD. Further studies are needed to elucidate the reliability and usefulness of the profile of subcortical atrophy in FTD to the process of differential diagnosis among FTD phenocopies.

Among the limitations of our study, we must consider that, notwithstanding MMSE represents the most commonly administered assessment for dementia severity in the world, with reliability and construct validity judged to be satisfactory [25], its usefulness have been criticized because MMSE scores were affected by age, education, and cultural background. Besides that, the use of a single linear measure of subcortical atrophy (BFI) may produce some confounding findings, mainly if we consider that the increase in BFI can results sometimes from natural deterioration with increased age. Finally, we should refer as a limitation the relatively few numbers of participants in the sample.

CONCLUSION

In conclusion, FTD group presented mean BFI scores above the cutoff for normal elderly population, indicating the presence of subcortical atrophy in this group. Besides that, mean BFI was higher (although not statistically significant) in FTD group than in dementia with EPS, which may suggest at least that subcortical pathology in FTD may be as important as in the dementia with EPS group.

Probably one of the most important findings of our work is that subcortical atrophy constitutes a good biological marker for cognitive deterioration in FTD and in dementia with EPS and is also a good marker for dementia severity in the latter group.

Subcortical atrophy was not correlated with age, educational level and functional ability (ADLs) in any of dementia groups analyzed.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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