CASE REPORT

Long-term prognosis of geriatric major depression in relation to cognition and white matter integrity: follow up of two cases

Prognóstico de longo prazo da depressão geriátrica em relação à cognição e à integridade da substância branca: acompanhamento de dois casos

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ABSTRACT

Introduction: The geriatric depression (GD) represents one of the most frequent psychiatric disorders in outpatient services specialized in old-age treatment. **Objective:** The course of two illustrative cases of GD is discussed, highlighting its clinical picture after antidepressant treatment and underlining variables related to disease prognosis, treatment effectiveness and conversion to major cognitive disorders such as vascular dementia (VD). **Methods:** The cognitive performance, depressive symptoms, autonomy and brain structural measurements as white matter hyperintensities (WMH) and hippocampal size, and microstructural integrity of WM with diffusion tensor imaging were followed during four years. **Results:** Case 1, with a severe degree of WMH, was associated with worsening cognition and increasing functional disability. Case 2, with mild WMH, an improvement of cognitive functioning could be seen. **Conclusions:** The existence of different subtypes of GD, as presented in this report, points a pathophysiological heterogeneity of GD, and suggests a possible *continuum* vascular depression (VaDp) and vascular cognitive impairment (VCI).

Keywords
Late life depression, geriatric depression, vascular depression, cognition, magnetic resonance imaging, diffusion tensor.

RESUMO

Introdução: A depressão geriátrica (DG) representa um dos mais frequentes transtornos psiquiátricos em ambulatórios especializados em idosos. **Objetivo:** Discutir a evolução da DG por meio de dois casos ilustrativos, destacando-se as variáveis relacionadas ao prognóstico da doença e à conversão para quadros cognitivos mais graves como demência vascular (DV). **Métodos:** Os casos foram acompanhados por quatro anos com medidas do desempenho cognitivo, funcional, sintomas depressivos, juntamente com as alterações de estruturas cerebrais, como hiperintensidades da substância branca (HSB), dimensões hipocampais, e a integridade microestrutural da SB, por meio de imagens com tensor de difusão. **Resultados:** Caso 1, com grave intensidade de HSB, evoluiu com piora cognitiva e funcional. Caso 2, com leve intensidade de HSB, evoluiu com melhora cognitiva após o tratamento da depressão. **Conclusões:** A existência de diferentes subtipos de DG, como apresentado neste relato, aponta para a heterogeneidade da fisiopatologia da DG, sugerindo um possível *continuum* entre depressão vascular (DpVa) e comprometimento cognitivo vascular (CCV).

Palavras-chave
Depressão tardia, depressão geriátrica, depressão vascular, cognição, ressonância magnética, tensor de difusão.

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INTRODUCTION

Late-life depression or geriatric depression (GD) represents one of the most frequent psychiatric disorders in specialized outpatient services[1] and affects nearly 9% to 18% of the general elderly[2,3]. GD may affect from 3.2% to 15.4% of the elderly Brazilian population[4,5].

The course of GD has shown to be rather heterogeneous[6], and it is assumed that the combination of white matter lesions and cognitive symptoms related to frontal lobe dysfunction might be associated to GD with specific features. This led to the concept of Vascular Depression (VaDp) hypothesis[7]. This condition proposed by Alexopoulos includes major depression occurring after 65 years of age, vascular risk factors and significant cerebrovascular disease, as main aspects, and cognitive impairment, represented by executive dysfunction, as a secondary aspect[7]. In some situations a spectrum of cognitive and behavioral impairment of vascular etiology, comprising vascular depression (VaDp), mild vascular cognitive impairment (VMCI), and vascular dementia (VaD) may be considered[8,9].

The affective symptoms and executive dysfunction are both related to disconnection of prefrontal-subcortical circuits[10]. Different frontal connections, such as the cortico-limbic-striatum-pallidum-thalamic-cortical circuits, have been shown to play an important role in affective modulation[11,12], contributing to the pathogenesis of some cases of late-life depression[13]. Noteworthy, frontal vascular lesions have shown to be associated with a poorer response to antidepressant treatment[14].

MR studies with diffusion tensor (DTI) acquisitions and fractional anisotropy (DTI-FA) are used to evaluate white matter integrity in psychiatric illness, such as depression[15].

This study aims to examine the heterogeneity of outcome patterns of GD. Two cases of depression, with behavioral, neuropsychological, and neuroimaging assessments followed up for four years are described as examples. The hypothesis of a *continuum* between VaDp and VCI (which includes VMCI and VaD) is analyzed, as well as the association between brain vascular lesions in specific regions and poor response to antidepressant treatment.

METHODS

Two cases of GD were assessed over a 4-year-period at the specialized geriatric outpatient unit (Centre for Alzheimer Disease and Related Disorders) of the Federal University of Rio de Janeiro (CDA/IPUB-UFRJ-Brazil).

The cases fulfilled Alexopoulous' criteria for vascular depression[7]. Hamilton Depression Scale[16] was applied to investigate depressive symptoms and the Neuropsychiatric Inventory (NPI) for a global evaluation of behavioral disturbances[17].

Cognitive, functional, and behavioral performance and staging were assessed, as well as neuroimaging, according to the protocol of vascular dementia (VaD) recommendations of the DNCE-ABN which include the Mini-Mental State Examination (MMSE), a validated Brazilian version of CAMCOG, executive function assessment (Trail-Making Test – TMT), Clock Drawing Executive Task – CLOX, and semantic verbal fluency – VF [category animals]). TMT A can be considered as an indicator of visual-motor speed (processing speed), and TMT B can be considered as an indicator of cognitive flexibility. CDR scale was used for staging of dementia Functional Activities Questionnaire (FAQ) was applied to evaluate instrumental activities of daily-living (IADLs). The Hachinski Ischemic Score (EIH) for stroke risk assessment was used. The evaluation of the severity of white matter hyperintensities (WMH) was performed with a modified Fazekas scale (mFazekas). De Leon score was applied to evaluate hippocampal atrophy[18].

The neuroimaging evaluation was performed with MRI of the brain at baseline and at the end of the follow up (over three years later) with a GE Signa Horizon (1.5 T) equipment for standard acquisitions (including FLAIR sequence), and diffusion tensor imaging (DTI), for fractional anisotropy measurements (DTI-FA). Post-processing of DTI was performed at a ADW 4.3 workstation with Functool 4.5.3 (GE Medical Systems) to obtain the quantitative values of DTI-FA.

RESULTS

The case 1 relates to a 73 years old, female with seven year of schooling who suffered from hypertension and *diabetes mellitus*. She reported that two years earlier she experienced her first episode of depression, which caused a negative effect on her capacity to look after herself, pessimism, sadness, and increased dependency of her daily life activities. At that time, Sertraline 50 mg was introduced, with good clinical response.

At the initial consultation at this clinic, she presented memory complaints. The neuropsychological assessment revealed impairment of cognitive performance, with low global CAMCOG and attention and abstract thinking subscales, and the tests for executive function, TMT and CLOX, suggested impairment of executive function. CDR was 0.5 (Table 1). MRI showed moderate intensity of WMH (mFazekas score = 2) (Figure 1A). De Leon score for hippocampus was within normal values (Table 2).

Over the four-year period the patient presented several episodes of depression, and progression of cognitive impairment, mainly of executive function. Sertraline was increased up to 200 mg/day for treatment of the relapse of depressive symptoms in the first six months. At the 6th month evaluation, the patient still showed intense depressive symptoms,

together with difficulty in dealing with daily-life activities, such as controlling her own medication, preparing meals, keeping up to date with community life (FAQ = 13). Sertraline was substituted for Venlafaxine, 150 mg/day, and by the end of the 1st year, the affective symptoms showed remarkable improvement. The patient did not return to the clinic during the second year, continuing the treatment in a local health clinic. On returning to the clinic, she reported two new episodes of depression, partially controlled with Mirtazapine 45 mg in association with Bupropion 150 mg. One year after her last evaluation, the patient showed a relapse of the depressive symptoms (Table 3). In the last year of the follow-up the patient´s depressive symptoms showed improvement. However, global CAMCOG and memory subscale remained low, as well as executive function. CDR increased from 0.5 to 1 (Tables 1 and 3).

A new MRI showed an increase of white matter load (mFazekas score = 3) (Figure 1B), while there were no hippocampal changes in comparison to the initial findings (Table 2).

The comparative results of the DTI-FA are seen bellow.

The case 2 is about a 67 years old, female, with three years of schooling, who was hypertensive but not diabetic, whose first interview revealed severe late-life depressive symptoms, started one year before, when her son died. The global CAMCOG score was about average, with lower scores on attention and abstract thinking subscales, as well as low scores on TMT and CLOX, compatible with executive dysfunction. There was a mild functional decline. CDR was 0.5 (Table 1).

The initial MRI showed low level WMH (mFazekas score = 1) (Figure 2A), while the hippocampal were in the normal range.

After being treated for depression with Sertraline, increased up to 100 mg, for one year, the depressive symptoms improved, accompanied by improvement in global CAMCOG and the subscales scores, as well as of executive function, and functional improvement. CDR was zero (Table 1). These improvements were sustained for the following 4 years (Table 1).

Table 1. Cognitive follow-up data

		Case 1		Case 2		Normative values (*)	
		BL	Year 4	BL	Year 4	Case 1	Case 2
CAMGOG global		74	69	78	91	83.52 (7.23)	76.11 (7.36)
CAMCOG subscales	Orientation	7	9	10	10	9.37 (0.81)	9.27 (0.78)
	Language	23	23	27	28	25.04 (2.13)	23.46 (2.02)
	Memory	18	15	19	19	21.44 (3.48)	20.70 (3.08)
	Praxis	11	9	10	12	9.78 (1.55)	9.42 (1.63)
	Perception	8	7	7	8	6.96 (1.36)	5.86 (1.38)
	Calculation	2	2	2	2	1.78 (0,50)	1.65 (0,48)
	Attention	3	3	3	7	5.00 (1,81)	4,27 (1.76)
	Abstract. Thinking	2	4	0	5	4.70 (1.95)	2.50 (2.10)
Executive Function Tests	Clox I/II	11/15	13/15	9/15	15/15		
	TMT-A (%)	70 (50%-75%)	85 (25%-50%)	165 (< 10%)	73 (25%-50%)		
	TMT-B (%)	360 (10%-25%)	859 (< 10%)	445 (< 10)	225 (10%-25%)		
	TMT-B/TMT-A	5.14	10.10	2.69	3.08		
FAQ		0	4	3	0		
CDR		0,5	1	0,5	0		

*Normative value by Bueno 2009[19].

TMT A: Trail Making Test A; TMTB: Trail Making Test B; Porteus Maze Test; VF: Verbal Fluency; CDR: Clinical Dementia Rating; FAQ: Pfeffer's Functional Activities Questionnaire.

Table 2. Neuroimage data

		Hippocampus (l/r) (de Leon *et al.*, 1993)	WMH modified Fazekas (Gouw *et al.*, 2008)	DTI-FA values	
				Frontal	Posterior
Case 1	Baseline	1/3	2	0.239	0.352
	Year 4	1/3	3	0.258	0.296
Case 2	Baseline	0/3	1	0.315	0.347
	Year 4	0/3	1	0.334	0.349
Control values [-1dp] [range]		0/3-1/3	0-1	0.313 ± 0.023 [-1dp = 0,290] [0.284-0.351]	0.394 ± 0.046 [-1dp = 0.348] [0.316-0.457]

Table 3. Behavioral follow-up data

Year	Case 1		Case 2	
	HAM-D	NPI	HAM-D	NPI
BL	5	8	20	14
0.5	15	38	1	3
1	2	9	5	6
3	18	16	2	0
4	7	28	1	0

HAM-D: Hamilton Depression Scale; NPI: Neuropsychiatric Inventory; BL: baseline.

At the end of this study, the patient was again submitted to MRI, which revealed a very slight increase of WMH, maintaining the same score (mFazekas score = 1) (Figure 2B), and no hippocampal changes were found (Table 2).

The comparative results of the DTI-FA are as follows.

Results of DTI-FA

The DTI data of both cases were submitted to post-processing to obtain DTI-FA values of the subcortical white matter, which were compared with a control sample of normal elderly individuals[22]. At the beginning of the study, case 1 presented frontal DTI-FA values significantly inferior compared to those of case 2 and to the control group. The evaluation 4 years latter showed a slight loss of frontal DTI-FA values in both case 1 and 2, in comparison to the control sample. A loss in the posterior white matter in case 2 was also observed (Table 2).

DISCUSSION

The evolution of GD may vary significantly[6], as shown by the illustrative cases. It is believed that in some situations the affective symptoms might be a response to psychological stress[23]. In other cases, however, it can be considered within a spectrum of cognitive and behavioral impairment of vascular etiology, comprising vascular depression and VMCI[9]. Some studies suggest that these behavioural symptoms may be the earliest signs of VCI in progress[8].

It may be difficult to distinguish between cases of depressed patients demonstrating initial signs of VCI and those whose cognition will improve to treatment with antidepressants. Executive function appears to be the most relevant element in patients with GD, and is outstanding manifestation in vascular depression. However, these affective symptoms may represent an important, confounding element in the interpretation of cognitive deficits in non-demented and demented patients[24]. Considering transversal studies, there is agreement about the frequent presence of executive dysfunction in DG[25]. However, results showed variability when considering the specificity of executive deficits associated with depression[26-29]. Thus, long-term follow-up of cases is fundamental in determining diagnosis.

Long-term follow-up permitted the assessment of the cases in the absence and presence of depressive symptoms. This made possible to clarify the role of affective symptoms in each case. The initial cognitive evaluation of case 1, in the absence of depressive symptoms, revealed executive dysfunction (TMT and CLOX, and CAMCOG subscales attention and abstract thinking). The reappearance of depressive symptoms during the third year was accompanied by a global cognitive worsening, as shown by global CAMCOG, and executive function lower scores (attention and abstract thinking, TMT and CLOX). In the last year the patient's depressive symptoms showed improvement. However, global CAMCOG and memory subscale remained low, as well as executive function.

The initial evaluation of case 2 showed high scores regarding depressive symptoms (Table 3) and executive dysfunction (TMT and CLOX) (Table 1), and impairment of attention and abstract thinking. These cognitive parameters improved with the improvement of the depressive symptoms in the long-term.

Both cases presented impaired cognition accompanied by depression. However, the cognitive evolution, as seen above, was different. Case 1, with severe levels of WMH, diagnosed as vascular depression, displayed MCI (CDR 0.5) with executive dysfunction, worsening over time, evolving towards a more advanced state of VCI (CDR 1). Case 2, with mild levels of WMH and GD, and executive dysfunction, evol-

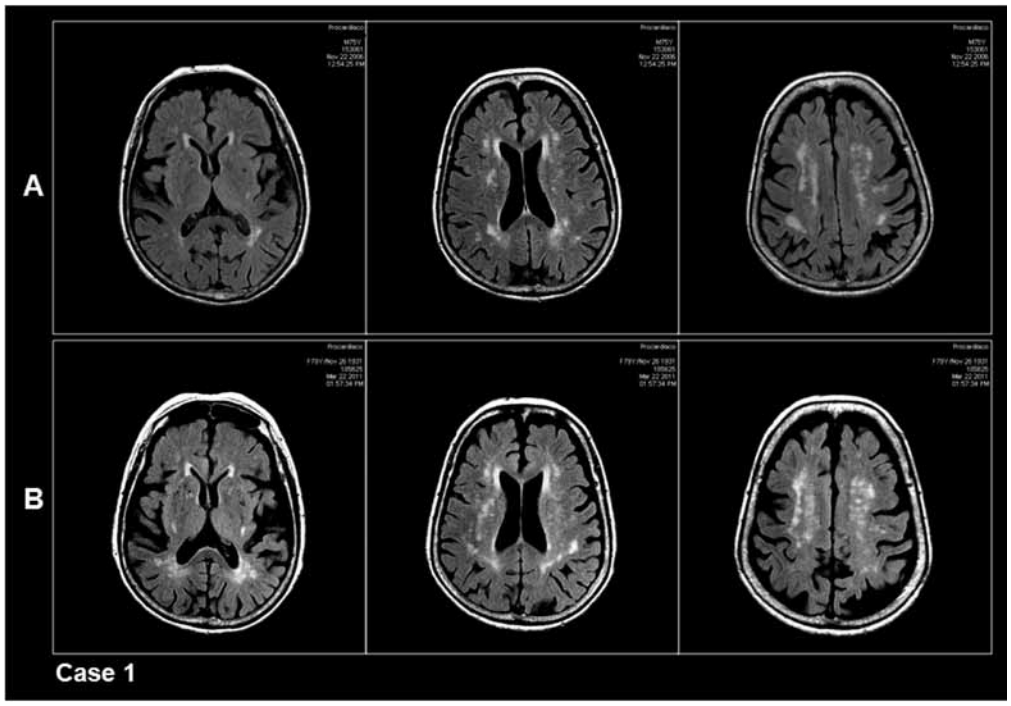

Figure 1. Case 1. MRI-FLAIR acquisition of three representative axial sections that show WMH burden. **A:** mFazekas score = 2; **B:** mFazekas score = 3.

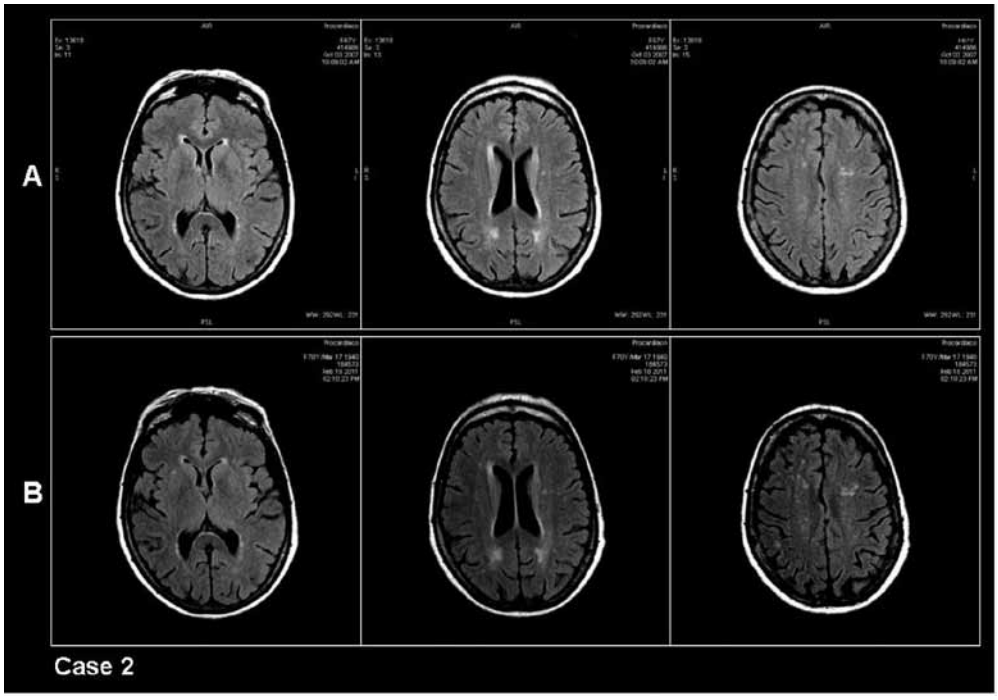

Figure 2. Case 2. MRI-FLAIR acquisition of three representative axial sections that show WMH burden. **A:** mFazekas score = 1; **B:** mFazekas score = 1.

ved to normalization of cognition (CDR 0). Patients with GD frequently demonstrate executive dysfunction, associated with difficulties in performing instrumental daily-life activities, which may persist even after the successful treatment of mood disorder. These particular patients, may, over time, develop VD[6].

For a better understanding of the relationship between the WMH and axonal integrity of the subcortical white matter, the neuroimaging evaluation was repeated at the end of the follow-up period. The present study shows evidence that a worsening of WMH lesions is associated with a worse prognosis for GD and cognitive decline. However there are few

studies demonstrating this relation[30-32]. Steffens *et al.*[33] described a patient with recurring GD over a 4-year period, which evolved to cognitive decline and VaD. This patient was also screened for the presence of WMH at the end of the follow-up, which showed worsening of the lesions[33]. Another study showed the same pattern with a two-year follow-up[34].

The comparison between the baseline and final neuroimaging studies were able to explain different patterns of GD. The lesions may contribute not only to the etiology of the affective symptoms and cognitive impairment in some case of GD[13,35], but also to a negative prognosis of the cases[36]. The DTI-FA values were reduced in the frontal white matter of case 1, and were in normal range in case 2, as compared to a normal group, which seems to be the determining factor for the different prognosis in each case. The posterior white matter showed reduced values in case 1, and remained in the normal range in case 2 (Table 2). Reduced DTI-FA values are related to loss of axonal integrity, and taking into account the frontal white mater. It is compatible with disconnection of prefrontal-subcortical circuits, considered the neuroanatomical substrate underlying affective and cognitive manifestations[10], and appear to have prognostic relevance in GD[14]. Other studies corroborate these findings, despite some variations[37,38]. The reduction of posterior DTI-FA values in case 1 is possibly related to the interruption of other circuits, not identified in the present study.

The two cases differed with regard to the time needed to show a response to treatment with anti-depressants, which is an important factor in defining the sub-types of elderly depression. Dew *et al.*[39] described four groups of patients with GD, each with different responses to therapy. The first group showed rapid improvement with the use of antidepressants (the best prognosis), the second, showed improvement, but required a longer period of antidepressant use, the third group demonstrated an oscillating course with improvement, and the fourth group proved to be resistant to treatment (the worst prognosis)[39]. In a recent study Alexopoulos *et al.*[14] evaluated 48 elderly depressed individuals (23 with refractory depression and 25 who responded to treatment with antidepressant medication). Just as described by Dew *et al.*, the case 2 of this study had a rapid response to treatment and evolved better, while case 1 showed a poorer response to antidepressant treatment with subsequent cognitive impairment.

CONCLUSION

The association of vascular factors (including vascular risk factors and WMH load) and GD has guided the development of the VaDp hypotheses and the mechanisms which predispose, initiate or perpetuate this subtype of depression. Neuroimaging studies, especially those with WMH assessment and quantitative DTI-FA have revealed the disruption of prefrontal-subcortical circuits. These changes might represent a neuroanatomical substrate associated with VaDp and the accompanying cognitive impairment, as well as influencing the kind of response to antidepressant treatment.

The existence of different subtypes of GD, as presented in this report, one with cognitive improvement and the other with cognitive decline, points out the pathophysiological heterogeneity of DG, and suggests a possible *continuum* VaDp and VCI (including VMCI and VaD), with significant impact on case management.

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