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BINSWANGER'S DISEASE AND QUANTITATIVE FRACTIONAL ANISOTROPY

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Abstract – **Objective:** To study the integrity of the white matter in Binswanger's disease (BD) patients with quantitative fractional anisotropy (DTI-FA). **Method:** Controls (12) and patients with BD (12) were included. Scans performed with MR (GE Signa Horizon/1.5T). Fazekas's score=6 with white matter hyperintensities extension ≥75% assessed on FLAIR scans. Standard parameters for DTI-FA were used. ROIs placed in symmetrical regions on two axial planes, data pooled in anterior (frontal) and posterior (temporo-parieto-occipital) regions. Analysis with Functool. Statistics for anterior and posterior regions comparison. **Results:** DTI-FA showed reduction of anisotropy, reflecting axonal damage and demyelination of fibers, more prominent in anterior in relation to posterior region, in BD patients in comparison to controls. **Conclusion:** Loss of integrity of fiber tracts reflects interruption of neural networks that subserve cognitive, behavioral, and motor integration. The more severely affected frontal region is related to executive dysfunction, a characteristic feature of Binswanger's disease.

KEY WORDS: Binswanger's disease, white matter, leukoaraiosis, diffusion tensor, fractional anisotropy.

Doença de Binswanger e anisotropia fracionada quantitativa

Resumo – **Objetivo:** Estudar a integridade da substância branca em pacientes com doença de Binswanger (DB) com anisotropia fracionada quantitativa (DTI-FA). **Método:** Incluídos controles (12) e pacientes com DB (12). Obtidas imagens de RM (GE Signa Horizon/1,5T). Escore=6 de Fazekas com hiperintensidades da substância branca com extensão ≥75% avaliados em imagens em FLAIR. Utilizados parâmetros padrão para DTI-FA. ROIs colocados em regiões simétricas de dois planos axiais, dados das regiões anterior (frontal) e posterior (têmporo-parieto-occipital) reunidos. Análise com Functool. Estatística para comparar regiões anteriores e posteriores. **Resultados:** DTI-FA mostrou redução da anisotropia, refletindo lesão axonal e desmielinazação de fibras, com predomínio na região anterior em relação à posterior, nos pacientes com DB em comparação aos controles. **Conclusão:** Perda da integridade de feixes de fibras reflete interrupção de redes neurais subjacentes à integração cognitiva, comportamental e motora. A região frontal, mais gravemente atingida, está relacionada à disfunção executiva, aspecto característico da doença de Binswanger.

PALAVRAS-CHAVE: doença de Binswanger, substância branca, leucoaraiose, tensor de difusão, anisotropia fracionada.

Binswanger's disease (BD) is one of the several subtypes of the vascular cognitive impairment-vascular dementia (VCI-VaD) continuum, with extensive white matter lesions as the main neuroimaging characteristic[1-4]. Initially described as a clinical-pathological report by Binswanger, and then by Alzheimer, until recently it was considered a rare subtype of VCI-VaD, and only amenable to diagnosis through postmortem examination[3,5-7]. Pathological examination shows brain shrinkage with hypotrophy and yellowish discoloration of the subcortical white matter. The microscopic neuropathology of the white matter lesions reveal mainly diffuse loss of nerve fibers, with axonal damage, demyelination and gliosis[3,5,8-10]. The number of nerve fibers per unit in selected areas of the white mat-

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ter is significantly reduced compared with that in the control group. The fibers tend to have thinner myelin sheaths. The pallor of the white matter is mainly due to loss of nerve fibers, and may be in part based on the thin myelin sheaths[3,5,8,9]. The large brain vessels show atherosclerotic changes, and the histopathology reveals microvascular changes in the form of severe arteriolar sclerosis, especially in the white matter[5]. This small-artery pathology is likely to be the underlying substract of such extensive white matter lesions, and is frequently related to hypertension, diabetes mellitus, dyslipidemia, and other vascular risk factors[11]. Among the many factors that may contribute to the development of these lesions, the most important are capillary loss, impaired cerebral blood flow autoregulation and hypoperfusion, arrhythmias and hypotension, changes in blood viscosity and coagulation state, and additionally the characteristics of the unique arterial blood supply of the hemispheric white matter. The ischemic injury that underlies the pathogenesis of the white matter lesions is possibly related to transient repeated events of drops in regional cerebral blood flow that induce an incomplete form of infarction[3,5,12-15]. Until recently, such information on the neuropathological changes underlying ischemic white matter damage was only available on neuropathological examination[8]. However, the development of the contemporary neuroimaging techniques (computer assisted tomography [CT] and nuclear magnetic resonance [MR]), has changed this situation. These techniques show a change of signal of the white matter lesions – in CT as hypodense areas, that led to the designation of leukoaraiosis (LA)[16], and on MR, as white matter hyperintesities (WMH), clearly seen on fluid-attenuated inversion recovery (FLAIR) weighted sequence. Both may be named LA to describe the diffuse white matter abnormalities on CT or MR brain scans, in the elderly and in association with vascular risk factors[17]. The microscopic neuropathological examination of the affected white matter showed by the neuroimage (CT and MR) revealed "ischemic leukoencephalopathy" in most cases, permitting to establish a relation between these white matter changes and ischemic lesions[7,9,12,15-18]. After the pioneer papers with CT[18] and RM[19] correlated with pathological examination there was an increase of the number of published cases. The opportunity to establish the diagnosis in vivo showed that this "poorly recognized vascular form of subcortical dementia" had a much higher prevalence than formerly thought[3-5,20], leading to the proposed concept of "senile dementia of the Binswanger type"[3].

Recently, more refined MR derived methods were developed so as to further analyze the white matter and its changes based on the diffusion tensor concept[21]. The diffusion tensor imaging (DTI) was developed taking advantage of the properties of the diffusion tensor, derived from the MR diffusion acquisition. This diffusion may be isotropic or anisotropic, and DTI permits to visualize the anisotropy and its degree. The method offers an opportunity to evaluate the brain white matter architecture in a qualitative and quantitative way, in normal and pathological states. Such a detailed analysis of the white matter with DTI is possible through two of its features – the mean diffusivity and the fractional anisotropy (FA). Currently, the most widely used measure of anisotropy is DTI-FA that allows for quantification, and the values obtained represent an average of the sampled fibers in a given region of interest (ROI). It is a highly sensitive but fairly nonspecific biomarker of neuropathology and microstructural architecture of white matter and is frequently considered as a marker of its integrity[22,23]. Several studies demonstrated that the organization of white matter fiber bundles is the basis for FA, the myelin appears to influence its measures, as well as axonal damage and loss. The parallel organization of white matter fiber bundles is the basis for anisotropic diffusion, whereas myelin appears to modulate the amount of anisotropy[22]. These fiber tracts are an essential part of the large neural networks that support cognition, behavior, and motricity. The interruption of these tracts disrupts these networks and leads to disconnection of the related structures. Such interruptions may cause disconnection syndromes, outstanding pathophysiological substracts of the VCI-VaD spectrum[9,23,24].

The objective of this study is to describe the status of the subcortical white matter in patients with Binswanger's subtype of VCI-VaD continuum with quantitative fractional anisotropy (DTI-FA), as compared with a normal control group.

METHOD

Subjects

The study included two samples, normal controls (n=12) and patients with Binswanger's disease (n=12). The inclusion of Binswanger's disease patients was according to NINDS-AIREN criteria[25]. All patients underwent a full MR protocol and the patients included herein had the highest scores of white matter lesions. The characteristics of the subjects are displayed in Table 1.

Techniques

A complete series of MR scans of the brain of the two samples was obtained with a 1.5T GE Signa Horizon machine, with standard and DTI acquisitions. FLAIR scans in the axial plane were examined to evaluate the extension of the white matter lesions, and were classified according to Fazekas's scoring system[21,26]. Only cases with score=6 and LA≥75% (visual assessment) were included. The scoring was performed by two of the authors in consensus (DMM, EE) (Fig 1).

The parameters used for the DTI-FA acquisition are in accordance to those found in international studies on the subject,

Table 1. Characteristics of the sample.

	NC	BD
n	12	12
Sex (m/f)	5/7	7/5
Age (range)	74.8±5.1	77.6±8.6
Education (years: m±sd)	12.4±2.43	9.67±4.56
NINDS-AIREN	Negative	Positive
MMSE[a] (score: m±sd)	27.4±2.70	20.2±5.37
CDR[b] (score)	0	1.50±0.64
Hachinski[c] (score)	0.92±0.79	8.75±4.14
Fazekas[d] (score)	2.0 ±0.85	6.0±0.0
Leukoaraiosis (extension %)	–	≥75%

NC: normal controls; BD: Binswanger's disease; [a]MMSE: Mini-Mental State Examination (short cognitive screening tool)[33]; [b]CDR: Clinical Dementia Rating Scale (global severity stages from 0 to 3)[34]; [c]Hachinski: ischemic score (clinical assessment of vascular risk)[28]; [d]Fazekas: white matter lesion scale (severity from 0 to 6)[26].

Table 2. Results of quantitative FA in NC vs BD.

Regions	ROIs (n)	FA units (mean±sd)	
		NC	BD
Anterior	96	0.3122±0.05	0.2396±0.07
Posterior	72	0.3937±0.09	0.2701±0.07
Total	168	0.3472±0.08	0.2527±0.07

NC: normal controls; BD: Biswanger's disease; ROI: region of interest; FA; fractional anisotropy.

and in the present study were as follows: TR/TE=10,000/89.1 msec, matrix=128×128, FOV=30×24 mm, NEX=1, *b*=1000 sec/mm^2, slice thickness=5 mm, number of slices=30 without gap. Circular ROIs of 60mm^2 were localized in 14 symmetrical regions of both hemispheres on two axial planes (parallel to the AC-PC line) of the DTI-FA maps (total number of ROIs=168 for each group) (Fig 2).

The DTI-FA maps were analyzed at an ADW 4.3 workstation using the Functool 4.5.3 (GE Medical Systems). The averaged values of the ROIs were pooled in anterior (frontal) and posterior (temporo-parieto-occipital) regions. Statistical analysis (basic, ANOVA)[27] was performed to compare intra-sample and inter-sample values of anterior and posterior regions.

Ethics

The present study is part of a larger project on Vascular Cognitive Disorder, approved by the Ethics Committee of IPUB-UFRJ. Informed consent was obtained from the participants or from a responsible family member before any study procedure.

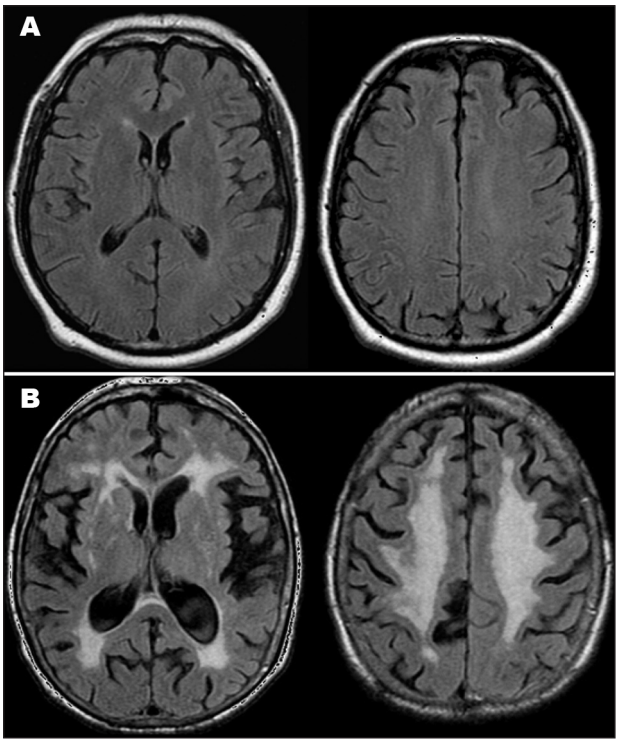

Fig 1. RM scans in FLAIR acquisition from [A] normal control and [B] Binswanger's disease patient. Left side – axial sections at basal ganglia level, right side – axial sections at supracallosal level. The images are examples from the samples of the present study.

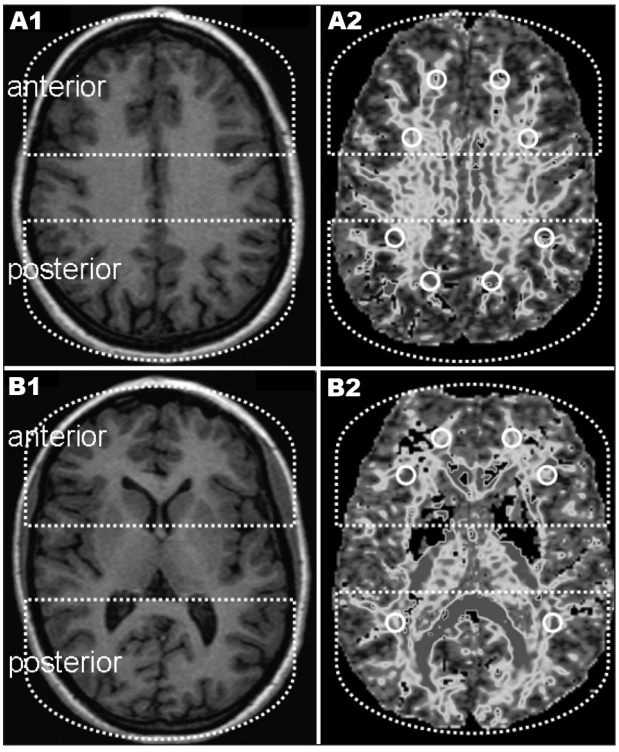

Fig 2. RM scans – axial sections at basal ganglia and supracallosal levels – in 3DT1 sequence [A1 and B1] and DTI-FA maps [A2 and B2] (in black and white). The T1 images are shown for topographical reference. The DTI-FA maps are shown to localize the ROIs placement. Interrupted lines circumscribe the anterior and posterior regions.

Table 3. Statistical significance as shown with ANOVA.

ANOVA summary					
Source	SS	df	MS	F	p
Rows[a]	0.26	1	0.26	52.96	<0.0001
Columns[b]	0.75	1	0.75	152.76	<0.0001
Rows × Columns	0.05	1	0.05	10.18	0.0016
Error	1.63	332	0		
Total	2.69	335			

[a]inter-sample (anterior and posterior regions – NC vs BD); [b]intra-sample (anterior vs posterior regions – NC and BD); NC: normal controls; BD; Biswanger's disease.

Table 4. Critical values for the Tukey HSD test.

	HSD [0.05]	HSD [0.01]
Rows (2)	0.02	0.02
Columns (2)	0.02	0.02
Cells (4)	0.03	0.03

HSD: Highest significant difference.

RESULTS

The DTI-FA data of NC vs BD are depicted on Table 2. The ANOVA results are shown on Table 3, and Table 4 shows the Tukey HSD Test.

The DTI-FA measures of the white matter were significantly reduced in BD sample in comparison to NC globally and between the anterior and the posterior regions (inter-sample). There was also a significant difference between the anterior vs posterior regions in each sample (intra-sample).

DISCUSSION

The diagnosis of Binswanger's disease could only be established through postmortem brain examination until a few decades ago. However, with the development of CT and MR the diagnosis in life was made possible[18,19]. In most cases, the ischemic cause of the white matter changes is suggested by high ischemic scores related to vascular risk factors, and confirmed by neuropathological examination[10,12,15,28]. These methods also increased in an expressive way the number of diagnosed BD (extensive ischemic LA/WMH) cases, formerly considered to be infrequent[3,4,20]. The development of DTI-FA has provided a qualitative and quantitative evaluation of the white matter, and the assessment of the integrity of its constitutive fiber tracts[22,23].

A global decrease of DTI-FA values of the white matter was found in the present study. There was also a differential change between the anterior and the posterior regions in Binswanger's disease patients as compared to normal controls (inter-sample), as well as significant changes between the anterior and posterior region in each group (intra-sample).

The literature on the issue is scarce. The bibliographical search yielded few international studies, and none in the national literature. The few DTI-FA studies on WMH with variable extension reported results in concordance with the ones described in the present paper[8,29]. Two papers were published specifically on BD, comparing this disease with normal controls (and Alzheimer's disease). The applied technique was the apparent diffusion coefficient (ADC), derived from the diffusion sequence, that represents the degree of diffusivity, and ADCs values and ratios (for the quantitative assessment of diffusion anisotropy) were calculated. These parameters were significantly higher in BD in comparison to normal controls in the anterior and posterior white matter representing an increase of diffusivity that reflects, according to the authors, a decrease of nerve fibers and diffuse myelin loss in the cerebral white matter lesions in BD patients. They also observed a regional difference, with values in BD being higher in the anterior regions of the white matter in comparison to the posterior ones[30,31]. These results are comparable to those of the present study, even considering the differences between the used techniques.

These findings are representative of an interruption of the numerous tracts that traverse the subcortical white matter. This interruption results in disconnection of the interrelated structures, maximally in BD. These fibers constitute the wide neural networks that subserve cognitive, behavioral, and motor integration, and their damage represents a certainly significant impact on the clinical performance of the patients in these functional fields[24].

The white matter changes were more significant in anterior (frontal) brain region in comparison to the posterior (temporo-parieto-occipital), with a suggestion of an anterior-to-posterior gradient, as already described[28]. Among the interrupted connections the cortico-cortical associative systems that converge on the frontal lobe are of critical importance, as well as the basal ganglia-thalamic-frontal circuits. The disconnection of the high-level frontal in-

tegrative region provides a structural basis for impairment of the executive function cognitive domain. As the anterior fiber systems in BD are affected in a prominent manner the presence of executive dysfunction in this subtype of the VCI-VaD spectrum appears as an expected and outstanding manifestation[29,32].

In conclusion, the neuropathological characteristic of extensive subcortical white matter ischemic lesion, as seen in Binswanger's disease, is axonal damage and myelin loss. These changes may be presently revealed by quantitative DTI-FA, an in vivo marker of fiber integrity.

All studied regions of the white matter of the brain of Binswanger's disease patients, anterior (frontal) and posterior (temporo-parieto-occipital), showed decreased DTI-FA values in comparison to normal controls. These findings are indicative of loss of integrity of fibers that cross the white matter, and reflect an interruption of fiber tracts, representing a disconnection process of the wide neural networks that are the basis of cognitive, behavioral, and motor integration. Such disconnection is one of the anatomic substrates that underpin the varied clinical manifestations that may be found. The frontal region is affected in a more severe way, compromising cortico-frontal and subcortico-frontal fibers that connect the high-level frontal integrative region, expressed clinically by executive dysfunction, a characteristic mark of the Binswanger's disease subtype of the VCI/VaD continuum.

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REFERENCES

1. Engelhardt E, Laks J, Cavalcanti JLS, et al. Demência vascular. Rev Bras Neurol 2004;40:5-25.
2. Erkinjuntti T. Subcortical ischemic vascular disease and dementia. Int Psychogeriat 2003;15(Suppl 1):S23-S26.
3. Román GC. Senile dementia of the Binswanger type. A vascular form of dementia in the elderly. JAMA 1987;258:1782-1788.
4. Román GC. Binswanger disease: the history of a silent epidemic. Ann N Y Acad Sci 2000;903:19-23.
5. Caplan LR. Binswanger's disease - revisited. Neurology 1995; 45:626-633.
6. Mast H, Tatemichi TK, Mohr JP. Chronic brain ischemia: the contributions of Otto Binswanger and Alois Alzheimer to the mechanisms of vascular dementia. J Neurol Sci 1995;132:4-10.
7. Tomonaga M, Yamanouchi H, Tohgi H, Kameyama M. Clinicopathologic study of progressive subcortical vascular encephalopathy (Binswanger type) in the elderly. J Am Geriatr Soc 1982;30:524-529.
8. Jones DK, Lythgoe D, Horsfield MA, et al. Characterization of white matter damage in ischemic leukoaraiosis with diffusion tensor MRI. Stroke 1999;30:393-397.
9. Yamanouchi H, Sugiura S, Tomonaga M. Decrease in nerve fibres in cerebral white matter in progressive subcortical vascular encephalopathy of Binswanger type. An electron microscopic study. J Neurol 1989;236:382-387.
10. Brito-Marques PR, Mello RV. Doença de Binswanger. Estudo anátomo-clínico de um caso [Binswanger's disease: case report]. Arq Neuropsiquiatr 1997;55:636-641.
11. Smid J, Nitrini R, Bahia VS, Caramelli P. Clinical characterization of vascular dementia: retrospective evaluation of an outpatient sample [Caracterização clínica da demência vascular]. Arq Neuropsiquiatr 2001;59:390-393.
12. Moody DM, Thore CR, Anstrom JA, et al. Quantification of afferent vessels shows reduced brain vascular density in subjects with leukoaraiosis. Radiology 2004;233:883-890.
13. Munoz DG. Small vessel disease: neuropathology. Int Psychogeriat 2003;15(Suppl 1):S67-S69.
14. Pantoni L, Simoni M. Pathophysiology of cerebral small vessels in vascular cognitive impairment. Int Psychogeriat 2003; 15(Suppl 1):S59-S65.
15. Young VG, Halliday GM, Kril JJ. Neuropathologic correlates of white matter hyperintensities. Neurology 2008;71:804-811.
16. Hachinski VC, Potter P, Merskey H. Leuko-araiosis: an ancient term for a new problem. Can J Neurol Sci 1986;13(Suppl 4): S533-S534.
17. O'Sullivan M. Leukoaraiosis. Pract Neurol 2008;8:26-38.
18. Rosenberg GA, Kornfeld M, Stovring J, Bicknell JM. Subcortical arteriosclerotic encephalopathy (Binswanger): computerized tomography. Neurology 1979;29:1102-1106.
19. Awad LA, Johnson PC, Spetzler RF, Hodak JA. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly. II. Postmortem pathological correlations. Stroke 1986;17:1090-1097.
20. van Gijn J. Leukoaraiosis and vascular dementia. Neurology 1998;51(Suppl 3):S3-S8.
21. Pantoni P, Simoni M, Pracucci G, et al. Visual rating scales for age-related white matter changes (leukoaraiosis): can the heterogeneity be reduced? Stroke 2002;33:2827-2833.
22. Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. Neurotherapeutics 2007;4:316-329.
23. Mori S, Zhang J. Principles of diffusion tensor imaging and its applications to basic neuroscience research. Neuron 2006; 51:527-539.
24. Catani M, Ffytche DH. The rises and falls of disconnection syndromes. Brain 2005;128:2224-2239
25. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN international workshop. Neurology 1993; 43:250-260.
26. Fazekas F, Chawluk JB, Alavi A, et al. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. Am J Neuroradiol 1987;8:421-426.
27. VassarStats: Statistical computation web site. http://faculty.vassar.edu/lowry/VassarStats.html (acessado em junho de 2008).

28. Hachinski VC, Iliff LD, Zilhka E, et al. Cerebral blood flow in dementia. Arch Neurol 1975;32:632-637.
29. O'Sullivan M, Morris RG, Huckstep B, et al. Diffusion tensor MRI correlates with executive dysfunction in patients with ischaemic leukoaraiosis. J Neurol Neurosurg Psychiatry 2004; 75:441-447.
30. Hanyu H, Shindo H, Kakizaki D, et al. Diffusion MRI study of cerebral white matter lesions in patients with Binswanger's disease]. Rinsho Shinkeigaku 1996;36:442-450. [Article in Japanese – Abstract acessed]
31. Hanyu H, Imon Y, Sakurai H, et al. Regional differences in diffusion abnormality in cerebral white matter lesions in patients with vascular dementia of the Binswanger type and Alzheimer's disease. Eur J Neurol 1999;6:195-203.
32. Masterman DL, Cummings JL. Frontal-subcortical circuits: the anatomic basis of executive, socail and motivated behaviors. J Psychopharmacol 2007;11:107-114.
33. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.
34. Hughes CP, Berg L, Danziger WL, et al. A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566-572.