AGE-RELATED CEREBRAL VENTRICULAR VOLUME CHANGES IN HEALTHY ELDERLY HUMANS

ALTERAÇÕES VOLUMÉTRICAS DOS VENTRÍCULOS CEREBRAIS RELACIONADAS A IDADE EM IDOSOS SAUDÁVEIS

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ABSTRACT

Introduction: Normal aging is associated with morphological alterations in brain. Ventricular system is located deep inside brain and reflect the overall process of parenchymal atrophy. Once neurodegenerative disorders course with more prominent dilatation of brain ventricles, to establish normative volumetric parameters from Brazilian healthy old individuals is necessary, and it may be an additional tool on differentiation from the normal to pathological. **Objective**: To investigate brain ventricular volume changes in Brazilian healthy elderly people. **Methods**: Transversal study using magnetic resonance imaging (1.5T) of the brain from 21 elderly healthy volunteers (67±6 years old). Data were assessed with manual segmentation technique. Regions of interest were the brain ventricles and intracranial volumes. Old (60-69 years old, 15 women) and Older (>69 years old) groups were created for analysis. **Results**: Volume of all ventricular compartments significantly increased (*p*<.001) with age, with exception of the fourth ventricle. The third and lateral ventricles increased between groups 2.1- and 2.8-fold, respectively. Mean total ventricular volume was 1.2±.4% of intracranial volume in Old and 3.2±1.8% in Older group (p<.001), which represents 15±6ml and 40±24ml (p=.001), respectively. We observed a moderate to strong positive correlation between ventricular volume and age, with the best correlation in the third ventricle (r=.710). Total intracranial volume diminished with age, but without statistical significance. **Conclusions**: Brain ventricles volume increased significantly with age in healthy old individuals, with exception of the fourth ventricle.

Keywords: brain atrophy; third ventricle; fourth ventricle; aging; magnetic resonance imaging

RESUMO

Introdução: O envelhecimento normal está associado a alterações morfológicas do cérebro. O sistema ventricular está localizado profundamente no encéfalo e reflete o processo global de atrofia do parênquima. Uma vez que doenças neurodegenerativas cursam com dilatação mais proeminente dos ventrículos cerebrais, estabelecer parâmetros volumétricos de normalidade em nossa população idosa saudável se faz necessário, podendo ser uma ferramenta a mais para diferenciar o normal do patológico. **Objetivo:** Investigar alterações volumétricas dos ventrículos cerebrais em brasileiros idosos saudáveis. **Métodos:** Estudo transversal com imagens de ressonância magnética (1,5T) do encéfalo de 21 idosos saudáveis (68±6 anos, 15 mulheres). Os dados foram examinados por técnicas de segmentação manual. As regiões de interesse foram os ventrículos cerebrais e o volume intracraniano. Criamos os subgrupos Idosos (60-69 anos) e Mais idosos (>69 anos) para a análise. **Resultados:** O volume de todos os ventrículos aumentou com a idade (p<0,001), com exceção do quarto ventrículo. O terceiro e os ventrículos laterais aumentaram 2,1 e 2,8 vezes, respectivamente, entre os grupos. O volume ventricular médio foi de 1,2±0,4% do volume intracraniano nos Idosos e de 3,2±1,8% nos mais idosos, o que representa 15±6ml e 40±24ml, respectivamente. Observamos correlação positiva de moderada a forte entre volume ventricular e idade, com a melhor correlação no terceiro ventrículo (r=0,710). O volume intracraniano diminui com a idade, sem significância estatística. **Conclusão:** os ventrículos cerebrais aumentam significativamente com o envelhecimento em idosos saudáveis, exceto o quarto ventrículo.

Palavras-chave: atrofia cerebral; terceiro ventrículo; quarto ventrículo; envelhecimento; imagem por ressonância magnética

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INTRODUCTION

Brain is a dynamic organ, and its dimensions vary in the lifespan of healthy individuals[1,2]. The volume reduction rates during the aging process are different in the various areas of the brain[3] and increase with age[4], the atrophy being more intense in the parietal, pre-frontal and temporal areas than in the occipital area[5,6]. Routinely visual and linear evaluation of brain imaging is commonly used to identify changes in both parenchyma and ventricles, as this qualitative type of approach is an easy and reliable method in the hands of well-trained radiologists. On the other hand, quantitative volumetric studies are more accurate in detecting subtle changes and are highly important in the experimental evaluation of specific differences between groups of healthy subjects and between healthy and unhealthy individuals[7].

Imaging studies of normal adult aging consistently show age-related enlargement of brain ventricles and the proportional reduction of gray and white matter volumes. Brain ventricles are well-delimited structures that are surrounded by brain parenchyma. Because of the more central location of ventricles in the brain, changes in their volumes could provide reliable information on the aging process. There is a consensus that in old people the enlargement of brain ventricles occurs as age increases and it reflects atrophy in the entire parenchyma.

Volumetry of the brain ventricles as an investigative technique probably began with the *postmortem* studies of Harvey[9]. Subsequently, *in vivo* data from computed tomography were used, but there were still some limitations that may bias data precision. There is now general agreement that magnetic resonance imaging provides the best relationship between anatomical representation and imaging definition simultaneously[10]. These advances in medical tools, especially in neuroinformatics, have contributed new data for the understanding of brain changes in healthy and nonhealthy elderly individuals.

In this study we set out to assess the changes in volume of brain ventricles in healthy elderly subjects, considering the scarcity of data on volumetric variation in ventricular volume of healthy subjects in the Brazilian population, the result of this study may be very important as a comparative reference providing normative data in healthy individuals to support the diagnosis of diseases with both brain and ventricular volume changes, such as idiopathic normal-pressure hydrocephalus and Alzheimer's disease.

METHODS

Volunteers

We assessed magnetic resonance images from 21 Brazilian volunteers over 60 years of age (67.7±6.3 years, 15 women), in a cross-sectional study. These subjects were considered healthy based on clinical and laboratory findings. Images from patients with a history of central nervous system disease, traumatic brain injury, psychiatric disorders, chronic alcoholism, delirium, GH deficiency, anemia, acute myocardium infarction, and uncontrolled hypertension were excluded, as well those with a history of use of central nervous system-action drugs.

Magnetic resonance imaging

Brain images were acquired on a 1.5 Tesla RM machine. The acquisition protocol included a sagittal echo--gradient T1-weighted sequence, with an isotropic voxel of 1 millimeter (MPRAGE 3D, repetition time of 9.7 ms, echo time of 4 ms) and 160 slices. Brain malformations, cysts or midline deviations observed in the images were exclusion criteria.

Manual segmentation process and anatomical limits

The manual segmentation was performed employing Display software (McGill University). This software allows assessing the regions of interest (ROIs) in the three anatomical planes and in a voxel-by-voxel manual technique, which results in a more precise study. Total intracranial volume (ICV) was calculated from magnum foramen to vertex. The volume is automatically calculated based on the number of voxels segmented as ROI. Age and gender of the volunteers were blinded to the observer during the segmentation process and reliability test.

ROIs in this study were brain ventricles. We assessed each ventricular compartment in sequence: left lateral ventricle (LLV), right lateral ventricle (RLV), third ventricle (ThV) and fourth ventricle (FV). For statistical purposes the sum of both lateral ventricles (BLV) was used. The transitional limits were (a) Monro's foramen was classified as part of the lateral ventricles; (b) the end of the third ventricle was the pons-mesencephalic junction; and (c) the end of the fourth ventricle was an imaginary line from the obex to the cerebellar tonsils. The choroid plexus and partial volume voxels were not regarded as ROI.

Statistical analysis

Based on age, we created two groups: O (O, 60-69 years old, 64.2±3.1, n = 15, 13 women) and "older" (OO, 70-79 years old, 76.3±2.7, n = 6, 2 women). We used linear regression and Pearson's or Spearman's correlation to assess changes in ventricle volumes with age, and Mann-Whitney's or Student's t-test for group comparisons and consonant applicability. Data analysis was performed using GraphPad Prism 5.0 software. A significance level of 5% was adopted.

In order to minimize the volunteers´ individual anatomo-physiological normal variabilities, we used corrected volumes, *i.e.*, ROI absolute volume percentage of the total ICV (corrected volume = ROI volume x 100 / ICV). The data are expressed as mean ± standard deviation.

Ethical aspects

This study was approved by Federal University of Pernambuco's Ethics Committee. All volunteers gave their informed agreement to participate.

RESULTS

Reliability

Three months after the first segmentation, we randomly reassessed 20% of our sample and observed an intra-observer correlation of .986 (95% CI = .955-.995, $p <$ .001, Spearman).

Total intracranial volume

The intracranial total volume mean was higher in the O group, but with no statistical significance (O: 1,304±106 ml; OO: 1,241±181 ml; p = .312, Student's t-test). The correlation age *vs.* total intracranial volume was weakly negative, also without statistical significance (r = - .204, p = .363, Spearman).

Lateral ventricles

We observed that there was a statistically significantly positive correlation between the corrected volume of the lateral ventricles and age (Table 1). When we compared corrected ventricular volumes between age groups, LLV was insignificantly smaller than the RLV (.77 vs. .80, p = .211, Wilcoxon) and we noticed a 2.9-, 2.7- and 2.8-fold volume increase between O and OO groups in the RLV, LLV and BLV (Table 3).

Table 1 – Linear regression and correlation of corrected volume vs. age

Variable		Lateral			Third	Fourth	TVV
		Left	Right	Both			
Linear regression	Slope F	15.2	16.5	14.5	26.9	0.9	16.7
	p	.001	< .001	.001	< .001	.369	< .001
	r^2	.444	.465	.434	.587	.043	.468
Correlation	r	.542	.612	.559	.710	.207	.596
	p	.011	.003	.008	< .001	.369	.004

r = Spearman. For Fourth ventricle, Pearson correlation was used. TVV = total ventricular volume.

Table 2 – Linear regression and correlation of absolute volume vs. age

Variable		Lateral			Third	Fourth	TVV
		Left	Right	Both			
Linear regression	Slope F	13.1	15.5	14.5	19.7	0.3	14.7
	p	.001	< .001	.001	< .001	.569	.001
	r^2	.408	.449	.434	.509	.017	.437
Correlation	r	.479	.579	.559	.651	.132	.566
	p	.030	.006	.008	.001	.569	.007

r = Spearman. For Fourth ventricle, Pearson correlation was used. TVV = total ventricular volume.

The absolute volumes of the LLV, RLV and BLV compartments were significantly larger in the OO group (Table 3) and also had a positive correlation with age (Table 2). The mean absolute volumes were 9.7 ml, 10.1 ml and 19.8 ml for LLV, RLV and BLV, respectively.

Third ventricle

Third ventricle, although a small and difficult ROI in manual segmentation, showed an intra-observer correlation of .998 (95% CI .934-999, p = .001, Pearson). The absolute and corrected volumes of this ROI were 2.1- and 2.3-fold, respectively, and larger in the OO group (Table 3), with statistical significance. Corrected volume linear regression was significantly and strongly positively correlated with age (Table 1). Regarding the 21 individuals the mean absolute volume was 1.1±.6 ml.

Fourth ventricle

This ROI is also difficult to manually segment, but showed an intra-observer correlation of .998 (95% CI .904-1.000, p = .002, Pearson). In spite of the fourth ventricle having shown an enlargement with aging (Tables 1

to 3) in corrected and absolute volumes, it was the only ventricular compartment that did not attain statistical significance in any of our analyses.

Total ventricular volume

Total ventricular volume (TVV) was the sum of all ventricular compartments. This ROI showed increases of 2.7- and 2.6-fold, respectively, in corrected and absolute volumes when we compared O with OO groups. This enlargement was statistically significant in correlation and linear regression with a moderate association between age and volume increment. We observed that there was an enlargement of around 2.0 ml per year in our sample. Figure 1 summarizes our data.

Table 3 – Old vs. Older groups comparisons for corrected and absolute volume

	Group	Lateral ventricles			Third	Fourth	TVV
		Left	Right	Both			
Corrected volume	O	0.48±0.22	0.52±0.24	0.99±0.44	0.06±0.02	0.09±0.02	1.2±0.45
	OO	1.5±.88	1.5±.86	3.0±1.7	0.14±.05	0.11±.03	3.2±1.8
	p	< .001	< .001	< .001	< .001	.216	< .001
Absolute volume	O	6.3±3.2	6.8±3.2	13.1±6.2	.82±.33	1.2±.3	15.1±6.4
	OO	18.3±11.9	18.2±11.1	36.4±22.9	1.7±.7	1.3±.5	39.5±23.8
	p	.002	.001	.001	.001	.439	.001

p = Student's t test. Absolute volume in ml.

DISCUSSION

We assessed brain ventricles for the purpose of evaluating the aging effects on these structures and identifying which one has the best correlation with the healthy aging process. Our data showed that brain ventricles enlarge with age. Lateral ventricles are asymmetrical, and RLV is slightly larger than LLV. The third ventricle showed the best correlation with age in absolute and corrected volume measurements, and the fourth ventricle was the only compartment in which statistical significance was not observed. The use of corrected volumetric data provided a better fitness in linear regressions than absolute measurements.

Brain hypotrophy is a physiologic and multifactorial process and courses with proportional ventricular dilatation. This hypotrophy is secondary to neuronal size contraction[11], activation of glia and synaptic diminishing[12], myelin loss and deposition of neurofibrillary tangles[13]. We found a significant increase in the volume of the brain ventricular system in healthy elderly people. This findings has already been described by others[4,14-18], but we did not find any study focusing on the enlargement of ventricular compartments in Brazilians. Studies on the Brazilian population are important since environmental, toxic and ethnic factors may be associated with ventricular volume changes[19]. Furthermore, others[20] concluded that individual genetics plays a central role in ventricular volume increase in elderly people.

We show a significant enlargement in all ventricular compartments except for the fourth ventricle. Similar findings[4,21] and also an insignificant reduction in fourth ventricle volume[2] throughout life have been described. The fourth ventricle may be less susceptible to atrophy since it has a direct relationship with older evolutionary structures or, as it is the only ventricle located in the posterior fossa, this region may create a different fluid dynamic or express a predominantly longitudinal (rather than centrifugal) pattern of atrophy, or the sum of these hypotheses. More studies are required to further understand this matter.

The volume of the third ventricle showed the best correlation in both corrected and absolute volumes *vs*. age in our data. In support to this, studies have shown an intense thalamic atrophy in healthy aging[11,22], and the best correlation between ventricular compartment and age[2], especially in men. Assessing this structure may be an important tool in the evaluation of aging; it is a relatively small ROI with a short time of segmentation and has an excellent intra-class correlation. In addition, others[23] have shown that the size of the thalamus did not differ in function of cerebral dominant side or sex. These data converge to draw more attention to third ventricle volume as an important parameter in the evaluation of healthy aging.

Some studies report significant asymmetry in brain structures[3,23], probably secondary to lateralized functions, while others do not[24]. In our data, lateral ventricles, showed a slight asymmetry in which the left side was smaller than the right; however, in the literature both similar[25] and opposite[3] findings are found. Although there are asymmetries, researchers[3] have shown that aging effects are equal on both sides; in support of that, our data show a difference of less than 5% between r^2-scores (.444 *vs*. .465; and .408 *vs*. .449 for corrected and absolute volume of left and right lateral ventricles, respectively). While different parenchymal areas have distinct rates of atrophy[11], the position of the ventricles and their plasticity to grow in any direction, depending on the tissue in contact with

them, tends to smooth those differences and represent the overall process of aging (parenchymal atrophy and ventricular system dilatation). Also, reports[26] show an increase in ventricular volume prior to detectable changes in the parenchyma.

Total ventricular volume is often assessed by researchers, and similar results have been obtained (Table 4). Indeed, the main variable associated with different results was age, but the male/female ratio and methodological differences may yield discrepant volumes. Our data on TVV was comparable with that of others and is an *ex vacuo* effect of parenchymal atrophy, even in healthy subjects. Studies suggest that in pathological conditions such as Alzheimer´s, the tissue loss is more prominent and a consequently greater ventricular enlargement[18]; this makes normative data relevant in differentiating the physiological aging process from pathological changes of brain tissue. Also, quantitative analysis of neuroimaging is progressively acquiring more diagnostic value[27-29]. Consonant with other authors[17], there is no significant change in total ICV.

As limitations, our sample, although quantitatively similar to that of others[17], is a small one and may not represent the entire elderly population. Likewise, there is no 1:1 male:female ratio that prevented an analysis by sex. Sex-related differences in brain structures is not unanimous[24], a good example of this is that Evan's index, a measure for normal-pressure hydrocephalus[30] does not consider sex.

Table 4 – Ventricular volumes (absolute in ml and corrected in %) in different studies

Reference	n	Age	Techinique	TVV	CVV
Amarki et al. 2010	46	71.0±6.0	RM 3.0 T – Manual	37.0±18.0	2.5±1.2
Blatter et al., 1995*	15	59.8±2.2	RM 1.5 T – Manual	24.2±12.2	–
Matsumae et al., 1996	22	72.0±5.0	RM 1.5 T – Semiautomatic	33.0±10.0	2.4±0.6
Carmichael et al., 2010#	52	83.6±4.4	RM 1.5 T – Automatic	30.7±12.6	–
Resnick et al., 2000	63	64.6±3.2	RM 1.5 T - Semiautomatic	25.2±10.8	–
This study	21	67.7±6.3	RM 1.5 T - Manual	22.1±17.3	1.8±1.4

TVV = total ventricular volume; CVV = corrected ventricular volume. *Only women data were used. #Prospectively healthy subjects.

CONCLUSIONS

Healthy aging occurs with a significant enlargement of the brain ventricles. All ventricular compartments, except for the fourth ventricle, increase in volume.

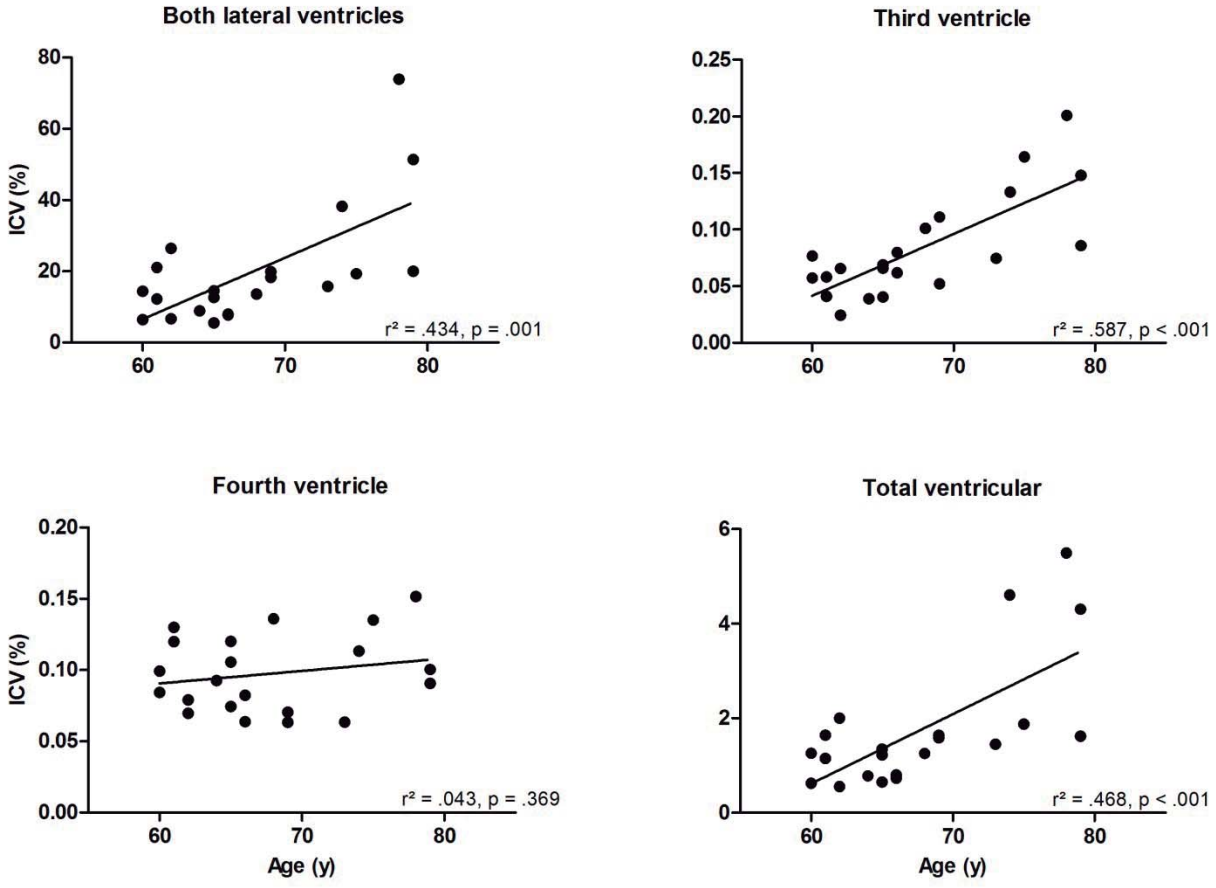

Figure 1. Linear regressions of both lateral, third and fourth ventricles and total ventricular volumes. ICV = intracranial volume.

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