ORIGINAL ARTICLE

Tables of percentiles of the third ventricle according to age and sex associated with brain aging

Katherine S. Hernández-Cortés[1], Adrián A. Pujals-Table[2], María Sagaró del Campo-Nelsa[3], and Pedrón Montoya-Arquímedes[4]*

[1]Department of Basic Biomedical Sciences, University of Medical Sciences of Santiago de Cuba; [2]Medical Biophysics Center, University of the East; [3]Department of Computer Sciences, University of Medical Sciences of Santiago de Cuba; [4]Neurophysiology Service of the Juan Bruno Zayas Alfonso Hospital. Santiago de Cuba, Cuba

Abstract

Introduction: *It has become essential to know the structural and cognitive changes that characterize the development of adults during aging and the biological roots of these changes to understand the transformations of the brain related to age and sex*. **Objective:** *The objective of the study was to determine the volumetry of the III ventricle according to age and sex, due to its wide use as a marker of cerebral atrophy as well as the elaboration of percentile tables that characterize this volumetry.* **Methodology:** *An analytical observational study was developed in 320 subjects with normal neurocognitive functions and neuropsychiatric examination, aged between 30 and 79 years, who underwent single-slice computed tomography of the skull. An image segmentation method was used based on the analysis of homogeneous textures and interpolation.* **Results:** *An increase in the volume of the third ventricle was obtained with respect to age. It was also demonstrated, the greater absolute volumes studied in men with respect to women. Based on these parameters, the mean values, confidence intervals, and percentiles of the lateral ventricles are described.* **Conclusions:** *The neuroimaging acquisition protocol implemented allowed us to obtain the volumetric parameters of the third ventricle in adults with normal global cognitive functions. These increased with the age. While sex had a significant effect, obtaining higher magnitudes in the male sex.*

Keywords: *Aging. Lateral ventricle volume. Computed tomography.*

Tablas de percentiles del tercer ventrículo según edad y sexo asociado al envejecimiento cerebral

Resumen

Introducción: *Se ha hecho indispensable conocer los cambios estructurales y cognitivos que caracterizan el desarrollo de los adultos durante el envejecimiento y las raíces biológicas de estos cambios para comprender las transformaciones del cerebro relacionadas con la edad y el sexo.* **Objetivo:** *Determinar la volumetría del III ventrículo según la edad y sexo, por su amplio uso como marcador de atrofia cerebral así como la elaboración de las tablas de percentiles que caracterizan esta volumetría.* **Metodología:** *Se desarrolló un estudio observacional analítico, en 320 sujetos con funciones neurocognitivas y examen neuropsiquiátrico normales, en edades comprendidas entre 30 y 79 años, a los que se le realizó tomografía computarizada de cráneo simple monocorte. Se empleó un método de segmentación de imagen basado en el análisis de*

***Correspondence:**
Katherine S. Hernández-Cortés
E-mail: ksusanahernandezcortes@gmail.com

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texturas homogéneas e interpolación. **Resultados:** *Se obtuvo un incremento del volumen del III ventrículo con respecto a la edad. Se demostró además, los mayores volúmenes absolutos estudiados en los hombres con respecto a las mujeres. A partir de estos parámetros se describe los valores medios, intervalos de confianza y percentiles de los ventrículos laterales.* **Conclusiones:** *El protocolo de adquisición de neuroimágenes implementado permitió obtener los parámetros de la volumetría del III ventrículo, en adultos con funciones cognitivas globales normales. Estos aumentaron con la edad. Mientras que el sexo tuvo un efecto significativo, obteniéndose magnitudes mayores en el sexo masculino.*

Palabras claves: *Envejecimiento. Volumen ventrículos laterales. Tomografía computarizada.*

Introduction

Knowing the normal measurements of the encephalic structures in the living human being is of great importance in the diagnosis and follow-up of various nosological entities[1-3]. Information on the precise measurements of these structures is insufficient. That is why there is a constant debate in the literature about the best method of measuring the various parts of the ventricular system[4].

With the introduction of modern machine learning techniques in neuroimaging, it has become possible to develop automatic classification systems and discover aging biomarkers. This fact, together with the advancement of computer systems, has made computerized axial tomography (CT) a key tool for cranial imaging[5,6]. However, most of the currently reported brain morphometry studies correspond to imaging studies of magnetic resonance imaging (MRI) techniques. Despite the CT images, they maintain their full validity in neuro diagnosis, still constituting the most widespread neuroimaging method internationally for being less expensive, to which is added that it is a much faster and less noisy test than MRI. Likewise, it is the neuroimaging technique with the greatest presence in the Cuban health system[7].

Due to the above, the present work is carried out to determine the volumetry of the third ventricle according to age and sex, due to its wide use as a marker of cerebral atrophy, as well as the elaboration of percentile tables that characterize this volumetry, which is It can be introduced in the clinic as a tool for the precise discrimination of the normality of the global volume of the lateral ventricles, in subjects with normal global cognitive functions.

Materials and methods

General characteristics of the investigation

An observational, analytical, cross-sectional study was developed in the period from February 2019 to December 2021 to complete the required sample size.

Universe and sample

All the patients expressed their willingness to participate in the study by signing the informed consent (Annex 1) and they turned out to have the neuropsychological examination and tomographic study of the head negative to the presence of old and/or recent intracranial lesions and with cognitive functions within normal limits, based on a score in the range of 24-30 as a result of the application of the mini mental state examination (MMSE) (Annex 2). Vulnerable groups such as pregnant women, groups with a gender identity different from their biological sex such as transgender people and people with diagnosed neurological and/or psychiatric diseases were excluded from the study.

Operationalization of variables

The variables studied were divided into main and secondary variables according to their importance in achieving the objectives of the study.

Main variable

Those that measure the volumetry of the cerebral ventricular structure studied were thus defined. The selected variable was expressed in cubic millimeters (mm^3). Volume of the III ventricle: The volume of the narrow medial cavity, located between the medial faces of the thalami, constitutes the cavity of the diencephalon composed of a roof, a floor, an anterior wall, a posterior wall, and two lateral walls.

Secondary variables

Age: collected in years completed at the time of the study according to identity card and grouped into five decennial intervals, having the lowest age as the lower limit and the older age as the upper limit.

- 30-39
- 40-49
- 50-59

– 60-69
– 70-79

Sex: according to the biological and phenotypic characteristics, it was divided into: male and female.

Obtaining the information

The main author was in charge of collecting the primary data and the variables included, by reviewing the outpatient medical records drawn up in the health areas and the reports of the CT scans of the skulls performed. Which were transcribed in a data form created for this purpose (Annex 3). To assess mental state, the MMSE was applied, an approved and standardized tool to detect, diagnose, and predict the evolution of cognitive impairment[7]. To obtain the images of the skull, the SHIMADZU brand single-slice helical CT scanner from the SIEMENS Company was used. The test time for the CT oscillated between 50 s and 60 s. Each patient received between 18 and 22 slices with a thickness of 5 mm. The matrix size of each segment was 512 × 512 pixels and the pixel size was 0.426 mm with a 16-bit gray level. All image processing and measurement were performed at the workstation by the members of the research team, supervised by a second degree specialist in Imaging.

Digital image processing

The technological tool iMagis, certified for its use by the National Center for Registration of medical equipment of the Ministry of Public Health of Cuba, was used[6]. For the morphometric estimates, the following steps were performed: pre-processing, feature extraction, and feature selection.

Pre-processing

The initial stage is the conversion of the image to a gray scale level. In the second step, the existence of noise and artifacts in the image is eliminated using the anisotropic diffusion filtering technique[8].

Feature extraction

It is performed based on the Gray Level Co-occurrence Matrix (GLCM), where the image is automatically divided into K clusters by estimating homogeneity features obtained from a co-matrix-occurrences[9-11].

Feature selection

The region of interest is segmented by combining texture information with the region growth approach. Finally, to evaluate the precision of the proposed approach, the Dice coefficient was used as a similarity metric and a value of 95% was achieved[12,13] (Fig. 1).

Validation of the measuring instrument

For the validation of the measurements through this application, a physical body called a dummy or phantom was used[14]. First, the technical conditions of the tomography were checked, the alignment of the table used was verified, the dummy was aligned on the tomography table, the protocol used for the head of an adult was applied, a configuration of 25 mA was used per second, 130 kV with duration of 8 s and cuts at 0.6 mm.

The topogram carried out had a length of 512 mm. The external and internal dimensions of the dummy were evaluated, in both directions (vertical and horizontal) using the tool offered by the Somaris/5 Syngo CT V40 system. Finally, we proceeded to check the measurements obtained using iMagis 3.0, obtaining the margins of error, which are shown in figure 2, being much lower than the reference values according to the thickness and size of the cut (Fig. 3).

The quantitative criterion of the segmentation was determined through the calculation of the Dice coefficient, which measures the degree of similarity between the sets. It is a normalized value that reaches values close to one when the match is large and close to zero when the match between the segmented region and the real one is low. In the partial validation of the segmentation in this research, it reached a value of 0.96[6].

Statistical analysis

Volumetric measurements were grouped according to age group and sex. They were summarized through descriptive statistics: arithmetic mean and standard error of the mean. Intervals for the 95% confidence mean were estimated. To identify possible differences between age groups and sexes, the possible correlation between the dependent variables that measure volumetric was first identified. Once the high correlation was verified, it was decided to use a multivariate linear model.

Finally, percentile tables of cerebral ventricular volumetry by age group for both sexes were made. The 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles were estimated with their 95% confidence intervals, for

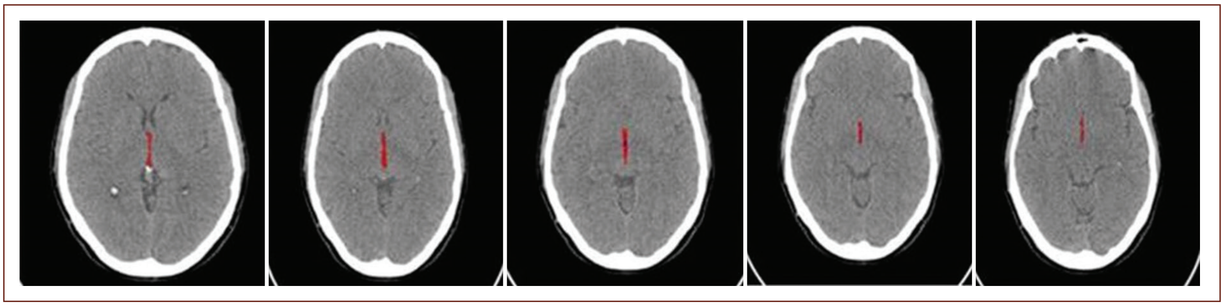

Figure 1. Segmentation of the third ventricle in computed tomography images.
Source: Collection of images in DICOM formats the Department of Imaging of the Saturnino Lora Hospital.

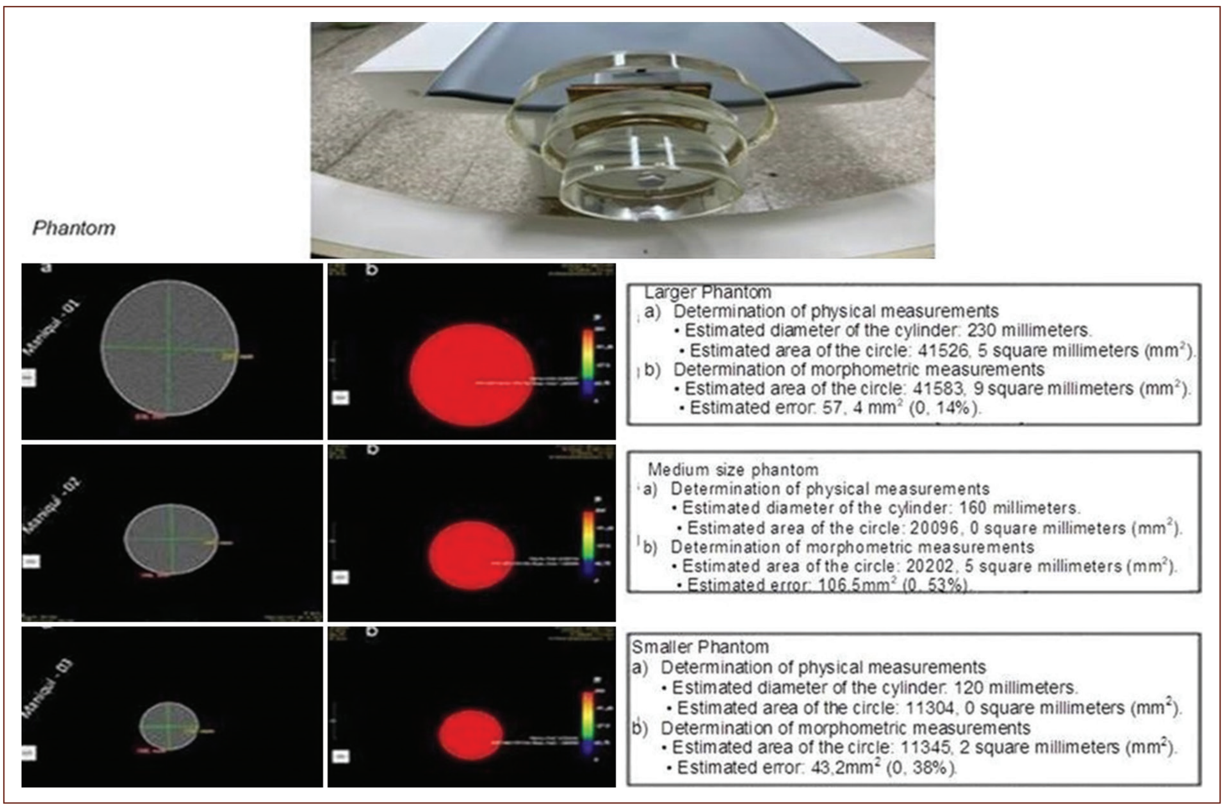

Figure 2. Percentile curves according to age and sex. The solid lines represent the exact values obtained and the lower and upper dashed lines, the lower and upper intervals, for a 95% confidence interval.
Source: Collection of images in DICOM formats the Department of Imaging of the Saturnino Lora Hospital.

which the standard error and bias between the measurement obtained in the study sample and that obtained from of the resampling applied for each volume. For greater precision and validity of the elaborated tables, a stratified random sampling with bootstrap replacement was used, all of which was done by automatic simulation.

Control of biases

The guarantee in the quality of the diagnosis and possible inclusion in the study was endorsed by a first degree specialist in neurology, who examined the central and peripheral nervous system in 100% of the included volunteers, all of which were negative, a

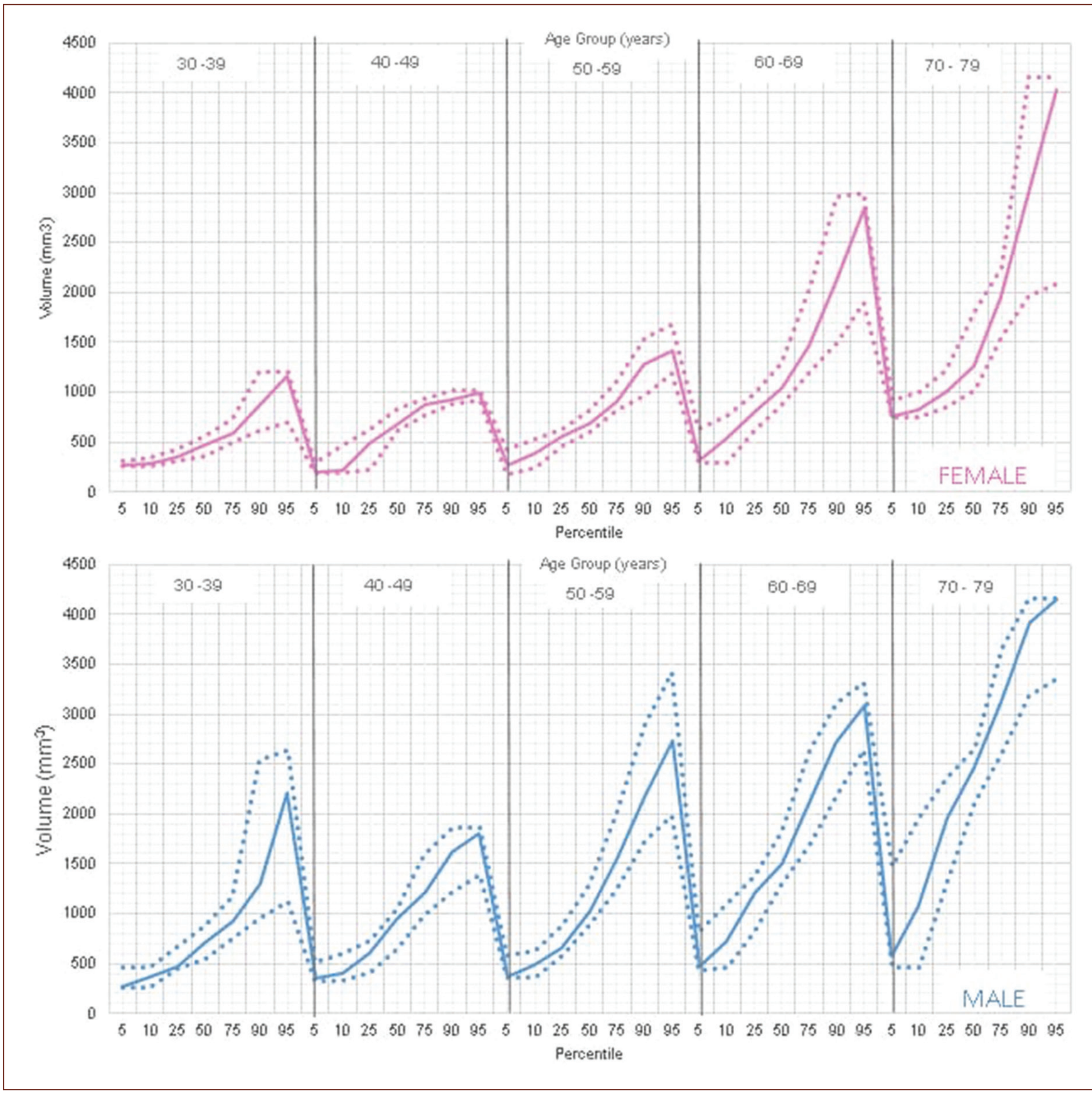

Figure 3. Determination of physical and morphometric measurements for validation of morphometry. The image in the center projects the physical mannequin or phantom used. The lower images in gray show the cylinders of the phantom scanned in the tomograph and those in red, the images obtained through iMagis 3.0. The tables reproduce the comparisons made of the physical measurements and those obtained by the technological tool used, as well as their margin of error.
Source: Collection of images in DICOM formats the Department of Imaging of the Saturnino Lora Hospital.

specialist a second degree specialist in neurophysiology evaluated the neuropsychological state of the patient and a second degree specialist in psychiatry ruled out the presence of psychiatric diseases. To minimize the bias of the observer and means of observation, the MMSE was applied by the first degree specialist in human anatomy, moments before the tomographic study.

Likewise, the same tomography, certified by the quality committee of the institution and under the established protocols, was used in the measurement. The CT scans performed were reported by a single second-degree specialist in Imaging. In the same way, all the measurements were made by the first degree specialist in human anatomy, through the iMagis 3.0 software, supervised by her main programmer and made the database to be processed.

Table 1. Summary measures for the volumetric variable

Volume (mm^3)	Mean	Error standard	Deviation standard	First quartile (Q1)	Median	Third quartile (Q3)
III ventricle	1136.2	43.2	772.1	604.6	900.0	1416.2

Medical bioethics

Before beginning the execution of the research, the approval of the project was received by the management of the participating hospital, its scientific council and its health research ethics committee. The inclusion and permanence of the subjects in the study were carried out under the voluntary principle, obtaining the written informed consent of all the participants. The confidentiality and protection of the data were maintained. The identity of the subjects was never revealed during the course of the investigation or once it was concluded. No personal information of the participants or their family members was disclosed. The subjects who participated in the study had previously indicated a simple head tomography; therefore the technique was not indicated for research purposes. Likewise, the subjects excluded from the study due to presenting alterations in neurological function or another health problem was referred to the corresponding specialties for evaluation and treatment.

Results

Table 1 shows the punctual estimate of the summary measures for the volumetric variable studied. The 95% confidence intervals of the mean and the standard deviation were estimated by resampling.

Table 2 and 3 shows the percentiles for female and male patients. It can be consulted in which percentile a certain individual is with cognitive functions within normal limits according to the measured volume, age, and sex of it. This query can be performed with 95% confidence for the volumes studied.

Figure 2 shows the values obtained for each percentile, according to the 10-year groups included and sex, represented in continuous lines. The lower and upper dashed lines show the lower and upper limits, according to age and sex.

Discussion

The skull computed axial tomography imaging protocol used in this study, associated with the third ventricle volumetric methods implemented in the IMagis 3.0 System, allowed obtaining a precise estimation of the volumetric parameters. Based on these parameters, the mean values, confidence intervals, and percentiles of the third ventricle are described. The main results of this study consisted in the report of an increase in the volume of the third ventricle with respect to age. It was also demonstrated, the greater absolute volumes studied in men with respect to women.

The sample analyzed was representative in quality and quantity. The selected ages have a lower limit of 30 years, since up to the age of 25 the nervous system is still developing and until the age of 30 the structural changes of brain aging have not begun to become visible radiological. The upper limit was established at 79 years because above this age irreversible atrophic changes have already occurred and their prevention is not achieved. Regarding quantity, we worked with a sufficiently large sample according to the statistical requirement.

Knowledge of the structural variations of the brain throughout life is important to better understand the factors that contribute to healthy aging and the risk of neurological conditions such as Alzheimer's disease[15,16]. Even so, we lack normative data on brain morphometry throughout adult life in large, well-powered samples. There is a consensus in the field of neurosciences that with increasing age, due to a compensatory mechanism to the decrease in brain volume, the volume of its cavities increases, which is generally larger in men than in women[17-19].

Despite the fact that morphometric studies are very common today, there is no robust scientific evidence for the use of percentile tables as a statistical statistician. Percentiles define the position of the individual with respect to the rest of the population in terms of a certain measure. Unlike the average that only gives us a central position, the percentile covers 100% of the possible locations of an individual with respect to the total population according to a certain measure, such as in this case, the volume[20].

Ching et al.[20] created normative percentile plots for MRI-derived subcortical volumes. Normative curves revealed volumetric loss with age, as expected, for all subcortical brain structures except for the lateral

Table 2. Point value and 95% confidence intervals for the percentiles of the total volumetry of the third ventricle measured in mm^3 according to age group (years) for the female sex

Volume (mm^3)	Age group (years)	Percentile	Value	95% confidence interval	
				Lower	Upper
III ventricles total volume	30-39	5	260.45	255.70	311.15
		10	289.70	255.70	341.50
		25	347.80	307.60	429.95
		50	473.80	362.40	553.10
		75	588.85	501.85	735.50
		90	869.20	616.90	1210.00
		95	1168.25	699.75	1210.00
	40-49	5	200.25	191.90	298.65
		10	217.00	191.90	462.50
		25	491.70	221.70	627.30
		50	679.50	615.10	831.20
		75	866.05	767.50	927.98
		90	931.00	882.10	1018.00
		95	995.35	919.55	1018.00
	50-59	5	258.00	181.00	419.00
		10	386.20	246.60	533.70
		25	553.15	466.10	621.97
		50	696.20	599.30	807.00
		75	905.40	807.00	1103.90
		90	1282.60	968.00	1545.70
		95	1421.95	1178.45	1672.50
	60-69	5	313.43	294.40	627.11
		10	532.87	297.86	760.50
		25	814.45	605.55	986.57
		50	1041.90	872.77	1292.25
		75	1463.23	1208.78	2048.28
		90	2098.65	1491.91	2964.40
		95	2855.50	1901.20	2988.60
	70-79	5	758.38	749.80	920.55
		10	818.06	749.80	1008.50
		25	1008.50	856.10	1219.40
		50	1263.60	1024.00	1819.10
		75	1958.60	1561.60	2242.30
		90	3035.32	1958.60	4149.70
		95	4032.56	2082.58	4149.70

Table 3. Point value and 95% confidence intervals for the percentiles of the total volumetry of the third ventricle measured in mm^3 according to age group (years) for the male sex

Volume (mm^3)	Age group (years)	Percentile	Value	95% confidence interval	
				Lower	Upper
III ventricles total volume	30-39	5	269.26	265.30	451.56
		10	375.02	265.30	467.88
		25	468.40	440.45	659.22
		50	699.35	542.40	885.15
		75	919.73	745.10	1161.88
		90	1288.03	942.90	2541.50
		95	2204.49	1114.60	2641.60
	40-49	5	355.90	329.30	514.26
		10	403.40	329.30	589.84
		25	603.20	405.30	737.90
		50	941.90	647.30	1046.70
		75	1219.50	981.60	1593.54
		90	1623.64	1219.50	1864.40
		95	1808.16	1392.82	1864.40
	50-59	5	375.24	352.90	573.38
		10	485.39	355.20	624.66
		25	649.70	573.40	882.50
		50	1031.20	881.70	1287.50
		75	1557.45	1234.56	1992.05
		90	2158.66	1728.30	2894.40
		95	2723.10	1977.54	3421.30
	60-69	5	467.55	426.60	816.48
		10	716.21	465.39	1105.95
		25	1206.30	813.43	1376.30
		50	1492.80	1285.10	1814.40
		75	2111.33	1690.10	2635.98
		90	2722.02	2185.46	3104.60
		95	3092.70	2639.72	3318.80
	70-79	5	567.58	468.50	1467.58
		10	1072.55	468.50	1970.55
		25	1956.83	1290.13	2357.15
		50	2466.20	2108.80	2661.50
		75	3122.98	2608.76	3646.05
		90	3909.95	3181.10	4161.60
		95	4143.95	3355.18	4161.60

ventricles, which expanded with age. Results similar to those demonstrated in this investigation. Likewise, it showed that subcortical volumes decreased faster in men than in women across the age range, but after the age of 60, fewer structures showed sex-dependent trajectories, indicating similar volumetric changes in men and women greater.

Cutler et al.[21] advocated in their study the use of normal percentile tables for head circumference, length, and weight, as they are well-established tools for clinicians to detect abnormal growth patterns. They developed a growth curve of cerebral ventricular volumes using a large number of normal pediatric brain magnetic resonance images. A graph with standardized growth curves was developed from this set of normal ventricular volumes representing the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles.

At present, there is no standard to assess the normal size or growth of the cerebral ventricular volume. Current standard practice is based on clinical experience for a subjective assessment of cerebral ventricular size to determine if a patient is outside the normal volume range. An improved definition of normal ventricular volumes would facilitate a more data-based diagnostic process, hence the relevance of using these percentile tables[22].

Vinke et al.[23], in this study, evaluated the differences between the percentile reference curves of the volumes of the subcortical structure of normal control subjects. They calculated percentile values in subcortical structures for individual patients from three cohorts, 91 mild cognitive impairment cases and 95 Alzheimer's disease cases and Alzheimer's Center patients, based on the distributions of each of the three cohorts. As part of their results, they found that the subcortical volume normative data from these cohorts are highly interchangeable, suggesting greater flexibility in the clinical implementation of the percentile curves obtained.

If one takes into account that the aging process is complex and even more so in the nervous system. The changes in the brain, from birth to the most advanced age, provide the nervous system with a great adaptive capacity to the influences and transformations of the environment, both internal and external. This process is known as neural plasticity or neuroplasticity and is considered one of the key biological mechanisms in successful aging[24-26].

We are of the opinion, from the perspective of basic and clinical neurosciences; the present study provides objective parameters to quantify the volumetry of the third ventricle through the standardization of global volumetric variables obtained by the voxel-based global brain volumetry method. The database of subjects with cognitive aging within normal limits is of scientific and practical value, as it constitutes one of the most extensive neuroimaging databases of which there are reports at a national level and the only one that is obtained through computerized axial tomography technique.

In the practical order, the tables of percentiles of the volumetry of the lateral ventricles are elaborated, with which a tool is introduced in the clinic that will make it possible to accurately discriminate the normality of the global volume of the third ventricle, which will allow comparisons to be made in the future of volumetry in patients diagnosed with neurodegenerative diseases to make timely diagnoses and follow-up of these diseases related to changes in the volume of the structures studied.

As limitations of this research we consider its cross-sectional design, in these studies, longitudinal designs where each individual serves as their own control, is preferable but they are also more difficult to achieve. Just as when using CT images, only global volumetric can be determined and not by specific regions of the brain.

We consider that the strength of this research lies in the design and application of a third ventricle volumetry protocol in single-slice CT images, based on the voxel-based global brain volumetry technique, which allows for accurate estimation of ventricular volume. Taking into account that many of the existing software and volumetric studies have been performed on MRI images, even though CT is the most used neuroimaging study nationally and internationally[4,6].

Conclusions

The present study provides a method of morphometric quantification of the volumetry of the lateral ventricles in which it is confirmed that age and sex have a significant effect on brain volume. In correspondence with their statistical behavior, they can be used as a standardized morphometric pattern in a population with normal neurocognitive functions and as a tool for individual diagnostic classification, but additional research is required to validate their possible clinical utility.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Supplementary data

Supplementary data are available at Revista Mexicana de Neurociencia online (10.24875/RMN.23000009). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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