Morphometric Analysis of Hemicerebellar Asymmetry with Central Vertigo Cases: A Stereological Study

Análisis Morfométrico de la Asimetria Hemicerebelar en Casos de Vértigo Central: Un Estudio Estereológico

"Nuket Gocmen-Mas, H.; ""Selim Karabekir; ""Ozge Yilmaz Kusbeci; ""Bunyamin Sahin; ""Tolga Ertekin; "Orhan Bas; "A. Canan Yazici & "Sevda Senan


SUMMARY: We aimed to evaluate the relevant methods of stereology to estimate hemicerebellar asymmetry according to sex in both adult right handed vertigo cases and comparing with healthy cases. The study included 14 adult control subjects and 18 patients with vertigo. The volumes of the cerebellar hemispheres were determined by MRI using the point-counting approach of stereological methods. The mean (±SD) of the right cerebellar hemispheres in the patients with vertigo were 52.49±5.42 cm³ in males, 50.11±4.02 cm³ in females. The mean (±SD) of the left cerebellar hemispheres in the patients with vertigo were 53.11±3.70 cm³ in males, 49.73±4.69 cm³ in females. There was not significant quantitative evidence detected in terms of cerebella asymmetry between sagittal plane estimates in the cases with vertigo in both genders (p>0.05). There were no statistically significant differences according to the genders between both vertigo and control subjects (p>0.05). There was only statistical significance between right and left hemispheres in male control subjects (p=0.039). There was no cerebella asymmetry between control and vertigo cases according to genders. The stereological evaluation of cerebella asymmetry or atrophy in humans correlate with gender is of importance for both clinicians and anatomists. The technique is simple, reliable, inexpensive and unbiased.

KEY WORDS: Cavalier principle; Stereology; Hemicerebellar asymmetry; Magnetic resonance imaging; Vertigo.

INTRODUCTION

Vertigo is an illusion of movement, usually rotation, although patients occasionally describe a sensation of linear displacement or tilt and it occurs when an imbalance or disturbance in vestibular function occurs anywhere in the peripheral and central vestibular system and it is associated with several different disorders. Asymmetric of neural activity between left and right vestibular nuclei is the most important reason of true rotator vertigo, where as more nonspecific vertigo symptoms are caused by cerebellar dysfunction, vasodepressor syncope, postural hypotension, cardiac dysrhythmia, peripheral neuropathy, anxiety, and hypoglycemia. Vertigo is always temporary and abates within a few days as central compensation occurs (Bruzzone et al., 2004; Weinberger et al., 1980). Signs and symptoms of dysfunction of neighboring structures include the central brainstem and cerebellar structures in central causes of vertigo (Brazis et al., 1990).

Several studies focused on the determination of brain compartments and tried to find MRI detectable discriminators of healthy and pathological aging in neurodegenerative diseases (Bernasconi et al., 2003; Ho et al., 2003; Edland et al., 2002). Asymmetric and volumetric changes in cerebellar anatomy has been an interesting subject
MATERIAL AND METHOD

Magnetic resonance image data. MR images of the subjects including 14 (7 men, 7 women) healthy control and 18 (8 men, 10 women) right handed adult patients with vertigo, aged between 26-50 years were examined, retrospectively. All subjects were admitted to the Department of Neurology and Neurosurgery in Afyon Kocatepe University Faculty of Medicine, with severe disturbances such as dizziness. All the patients underwent auto neurological examination, auditory evoke potentials registration and MRI. The patients with cerebrovascular disease, Multiple Sclerosis, Epilepsy, cerebellar or cerebellolateral point angle tumors, spondylosis, depressive state, poor vision, orthostatic hypotension, whiplash injury, vestibular disorders such as neuritis, peripheral cochleovestibular syndromes etc. or low cerebrospinal fluid syndrome were excluded. Inform contents of the patients both study and control groups were obtained.

Standard T1-weighted axial and sagittal plan (5 mm) slices were obtained at the suggestion of radiology specialist, and were used in order to compute the cerebellar hemisphere volumes in a 1.5-T MR machine (Philips Systems, Netherlands). A spoiled pulse gradient recalled (SPGR) acquisition in the steady state was used. This is a three dimensional volume gradient echo pulse sequence that is radiofrequency spoiled. A sagittal localizer was first acquired, and the volume of interest was then arranged to include the whole brain. The three-dimensional SPGR sequence was acquired over a period of 14 min. The MRI parameters were as follows; time of repetition (TR) of 35 ms and a time echo (TE) of 15 ms; the echo was 1/1 with 16 kHz. The flip angle was 35°. Because image data were collected retrospectively, the data set contained image matrix: Matrix of 256 × 256 pixels ×124 slices for a FOV of 24 × 24 × 18.6 cm, respectively. Thus, image voxels are 0.09375 × 0.09375 × 1.5 cm.

Stereological analysis. Both whole and hemicerebellar volumes computed from each image were measured three times by three observers using a stereological method. All measurements were performed blinded to subject details and the results of any other measurements. An optimal plan was taken as the smallest diameter of anisotropic structures that can be measured in volumetric analysis of sagittal and axial cranial MRI sections. Original MR Images were exported as if image files and further stereological analysis were done using these image sets with the aid of Image-J software. A
uniform point-grid with a point-associated area of 0.625 cm²
was randomly superimposed on each MR image using the
“Grid” plug-in installed with Image-J. Points hitting the
cerebella were manually counted for volume estimation.
Volume estimation was accomplished by the Cavalier’s
principle as described previously (Acer et al., 2008; Ekinci
et al., 2008; Kalkan et al., 2007; Sahin & Ergur) using the
formula given below:

\[ V = t \times \frac{[(SU) \times d]}{SL} \times SP \]

where, \( t \) is the section thickness, \( SU \) is the scale unit (the
real length of the scale marked on the MRIs), \( d \) is the distance
between two points in the point grid, \( SL \) is the scale length
(the actual measure of the scale on MRIs) and \( P \) is the
number of points counted. All data have been entered in a previously-
prepared Microsoft excel spreadsheet for automatic
calculation of both the results of the above formula and the
statistical evaluation parameters including the nugget
variance and the coefficient of error (CE).

In order to evaluate the hemispheric asymmetry
between cerebellar hemispheres, middle sections were
identified by the clear visualization of the cerebral aqueduct.
The point counts belonging to the middle section is divided
by two and the results were added to the total point counts
for each hemisphere separately, and thus, a volume value
for each cerebellar hemisphere has been estimated. The
stereological point counting method has been demonstrated
in Fig. 1. Statistical analyses were made afterwards and the
results were standardized to generate a normal database.

Statistical analysis. Distributions of the variables were
analyzed by Shapiro-Wilk normality test. Homogeneity of
the groups’ variances was controlled by Levene’s test.
Parametric test assumptions were satisfied, and differences
between left and right cerebellum volume means of control
and vertigo groups according to sex were analyzed by Three
Factorial Repeated Measures Analysis of Variance. Results
have been expressed as numbers of observations (n) and
mean ± standard deviation (SD). p value less than 0.05 was
considered as statistically significant. All statistical analyses
were performed with the SPSS software (Statistical Package
for the Social Sciences, version 13.0, SSPS Inc, Chicago,
IL, USA).

RESULTS

Mean values for hemispheres of cerebella volume
calculated according to stereological point counting method
are listed in Table I. The mean (±SD) of right cerebellar
hemispheres (RCH) in control group were 46.50±4.84 cm³
in males, 48.47±9.56 cm³ in females in sagittal plane. The
mean (±SD) of the left cerebellar hemispheres (LCH) in
control group were 51.56±4.17 cm³ in males, 52.33±5.52 in
females in sagittal plane. The mean (±SD) of the RCH in
the patients with vertigo were 52.49±5.42 cm³ in males, 50.11±4.02 cm³ in females in sagittal plane. The mean (±SD) of the LCH in the patients with vertigo were 53.11±3.70
cm³ in males, 49.73±4.69 cm³ in females in sagittal plane.
There was no significant quantitative evidence detected in
terms of cerebellar asymmetry between sagittal plane
estimates in the cases with vertigo (p>0.05). There were also
no statistically significant differences according to the
genders between both vertigo and control subjects (p>0.05).
There was only statistical significance between right and
left hemispheres in male control subjects (p=0.039).

![Fig. 1. The method of counting points has been demonstrated on a
sagittal brain MR imaging section](image)

Table I. Mean values of control and study groups’ cerebellum hemispheres according to gender. *p<0.05.

<table>
<thead>
<tr>
<th>Cerebellum</th>
<th>Control Mean ± SD</th>
<th>Vertigo Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left side</td>
<td>Right side</td>
</tr>
<tr>
<td>Male</td>
<td>n=7</td>
<td>51.56±4.17*</td>
</tr>
<tr>
<td>Female</td>
<td>n=7</td>
<td>52.33±5.52</td>
</tr>
</tbody>
</table>
DISCUSSION

Neuroanatomical, neuroimaging and behavioral reports of cerebella in cognitive and language functions increasingly enclose the cerebellum as the site of morphological changes occurring in neuropsychiatric diseases (Bruzzone et al.; Traccis et al.; Weinberger et al.).

MRI analysis allows determining quantitative analysis of cerebella and morphological evaluation of brain in vivo (Acer et al.) Many authors evaluated volume changes of cerebellum according to age and gender in healthy subjects. They claimed that female subjects had significantly smaller cerebellar volumes compared with males of similar age (Carne et al., 2006; Tang et al., 2001). Gocmen-Mas et al., found that the reduction of the cerebellar volume was not statistically significant and there was no cerebellar asymmetry according to age and gender in healthy subjects. The relationship of the gender of the subject and cerebellar size is not clear and there are conflicting reports in the literature (Acer et al.; Sim et al.; Escalona et al., 1991). Although the literature includes many studies about volume changes of cerebellum according to age and gender, there is no data about hemicerebellar asymmetry related to gender in adult cases of vertigo. Some pathological conditions such as cerebellar hypertrophy, atrophy, agenesis and architectural alterations could also cause asymmetrical changes between right and left hemispheres (Gocmen-Mas et al.; Sato et al.)

Asymmetric alterations of cerebella can lead to much different pathologies. Hemicerebellar asymmetric enlargement was reported in intractable epilepsy (Sato et al.). Unilateral atrophy of a cerebellar hemisphere occurring as a sequel of ischemic or destructive injury was reported. They investigated age-related atrophy of cerebellum by MRI using stereological methods in older people (Rollins et al., 1995; Tang et al.) Thus, we aimed to evaluate whether cerebellar hemispheric asymmetry is present or not in the cases of vertigo. Thus, mean values for hemispheres of cerebella volume was calculated according to stereological point counting method.

In morphometrical studies, the volume of an organ or its components, the volume of the variable component in a structure are frequently investigated via different measurement techniques (Kalkan et al.; Luft et al., 1998; 1997; Andreasen et al., 1996; Andersen et al.; Andersen & Pakkenberg). In the present study, we used the stereological method for the estimation of cerebellar asymmetry according to gender in the adult cases with vertigo since the previous study showed that the method (Gocmen-Mas et al.; Acer et al.). Cavalier principle of stereological approaches by point counting consists of overlaying each selected section with a regular grid of test points, which is randomly positioned. The Cavalier theorem of systematic sampling in combination with point counting is considered a reliable, simple, inexpensive and efficient method for estimating volumes in MRI (Gocmen-Mas et al.; Acer et al.; Cruz-Orive et al., 1983). However, the safest method is undoubtedly to reduce section thickness as much as technically possible while maintaining an acceptable image quality.

Ekinci et al. used MRI obtained from 24 normal volunteers ranging from 20-25 years of age and measured total brain, cerebrum and cerebellum volume. They found that the mean cerebellum volumes were 117.75 in males and 111.83 cm$^3$ in females (Ekinci et al.). They also claimed that cerebellar volumes were slightly larger in females but smaller in males than those reported by Escalona et al., 104 cm$^3$ in female and 122 cm$^3$ in male and Rhyu et al., 115.4 cm$^3$ in female and 126 cm$^3$ in male smaller than those of Luft et al. mean 134.3 cm$^3$ in both sexes and similar to Dupuis (Ekinci et al.; Rhyu et al., 1999; Luft et al., 1998; 1997; Rollins et al.; Escalona et al.). It’s not clear that discrepancy may be due to the racial difference or is the due to the variation resulting from different scanning protocols and measuring methods used. Ekinci results revealed that the volumetric composition of the cerebellum does not show sexual dimorphism. We found that right hemisphere of cerebellum was smaller than the left in control male subjects. There were no asymmetric differences in vertigo for either sexes. The present evaluation of cerebella hemisphere volumes can be done on any complete set of MRI, where plane scan distance and magnification factor is known, which already take place on the MRI. The stereological evaluation of hemicerebellar asymmetry or atrophy in humans correlate with sex is of importance for both clinicians and anatomists. The technique is simple, reliable, unbiased and inexpensive. The data of the present study can large enough to be meaningful for anatomists and clinicians. Further studies are required with larger samples in order to support these data.

RESUMEN: Nuestro objetivo fue evaluar los métodos relevantes de estereología para estimar la asimetría hemicerebelar según el género, tanto en adultos diestros, casos de vértigo y al compararlos con casos control. El estudio incluyó a 14 sujetos adultos como control y 18 pacientes con vértigo. Los volúmenes de los hemisferios del cerebelo se determinaron en la RM utilizando el recuento de los puntos del método de estereología. La media (±DE) de los hemisferios derecho del cerebelo en los pacientes con...
vértigo fueron 52,49 ± 5,42 cm³ en los hombres, 50,11 ± 4,02 cm³ en las mujeres. La media (± DE) de los hemisferios izquierdo del cerebelo en los pacientes con vértigo fueron 53,11 ± 3,70 cm³ en los hombres, 49,73 ± 4,69 cm³ en las mujeres. No hubo evidencia cuantitativa importante detectada en cuanto a la simetría entre las estimaciones del cerebelo entre plano sagital en los casos con vértigo en ambos sexos (p > 0,05). No hubo diferencias estadísticamente significativas según los géneros entre ambos el vértigo y los sujetos control (p > 0,05). Sólo hubo significancia estadística entre los hemisferios derecho e izquierdo en los sujetos control masculino (p = 0,039). No hubo asimetría entre el cerebelo control y de los casos el vértigo de acuerdo a los géneros. La evaluación de la simetría estereológica o atrofia del cerebelo en el ser humano se correlaciona con el género es de importancia para los clínicos y anatómicos. La técnica es simple, confiable, de bajo costo e ímparcial.

PALABRAS CLAVE: Principios de Cavalieri; Estereología; Asimetría hemicerebelar; Imagen por resonancia magnética; Vértigo.

REFERENCES


Correspondence to:
H. Selim Karabekir , MD
Kocatepe University
Faculty of Medicine
Department of Neurosurgery
Afyonkarahisar
TURKEY

Tel: +90 272 2463301
Fax: +90 272 2463300

Email: hskarabekir@hotmail.com

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