

# Stereological volumetric evaluation of the cerebellum in benign paroxysmal positional vertigo

*Nuket Gocmen-Mas, PhD, Orhan Kabveci, MD, Selim Karabekir, MD, Ozge Y. Kusbeci, MD, Ali Altuntas, MD, Ayse C. Yazici, PhD.*

## ABSTRACT

**الأهداف:** تقييم تغيرات حجم المخيخ واختلال تماثل نصفيه الأيمن والأيسر لدى المرضى المصابين بالدوار الوضعي الانتيابي الحميد.

**الطريقة:** أُجريت هذه الدراسة في عيادة الأذن والحنجرة بقسم جراحة الأعصاب والعلوم العصبية، كلية الطب، جامعة كوكاتيب، أفيونكاراهيستار، تركيا، واستمرت خلال الفترة من يناير 2004م إلى ديسمبر 2008م. لقد قُسم المشاركون في الدراسة إلى مجموعتين متماثلتين في الجنس والعمر وهما: مجموعة الدراسة (15 مريضاً) وشملت المرضى المصابين بالدوار الوضعي الانتيابي الحميد، ومجموعة الشاهد (14 مريضاً). وتم تقييم التغيرات التي طرأت في حجم المخيخ وتماثل نصفيه الأيمن والأيسر باستخدام طريقة التجسيم في صور الأشعة.

**النتائج:** أشارت نتائج الدراسة إلى أن المخيخ الأيمن لدى المشاركين في مجموعة الدراسة والشاهد قد كان أصغر حجماً من المخيخ الأيسر، وبالمقابل لم يكن هناك اختلافاً كبيراً في أحجام المستوى المحوري والسهمي لدى المرضى في مجموعة الدراسة. كما لم يكن هناك اختلافاً كبيراً في أحجام المخيخ الأيمن والأيسر بين مجموعة الشاهد والدراسة ( $p=0.023$ )، بالإضافة إلى ذلك لم يؤثر كلاً من العمر والجنس على تماثل نصفي المخيخ وضمورهما بين مجموعة الدراسة والشاهد.

**خاتمة:** أثبتت هذه الدراسة بأنه لم يكن هناك اختلافاً في ضمور أو تماثل نصفي المخيخ بين مجموعتي الدراسة ومجموعة الشاهد التي تماثلها في العمر. وتعد طريقة تجسيم نصفي المخيخ لتقييم ضمورهما وتماثلهما مهمة جداً لكل من الأطباء والمشرحين، كما تعد هذه الطريقة بسيطة، وغير مكلفة، ويمكن الاعتماد عليها.

**Objective:** To evaluate cerebellar volume changes and the asymmetry of patients with benign paroxysmal positional vertigo (BPPV).

**Methods:** The cerebellar hemispheres' volumetric symmetry were evaluated using a stereological method on MR images. The study included 15 patients with BPPV, and 14 age-, and gender-matched control

subjects. The cases were admitted to the Departments of Otolaryngology, Neurology, and Neurosurgery in the Faculty of Medicine, Kocatepe University, Afyonkarahisar, Turkey with the complaint of vertigo between January 2004 and December 2008.

**Results:** The right hemi cerebellum volumes of the subjects with BPPV and the controls were measured smaller than the left hemi cerebellar volumes, however, there was no statistically significant quantitative evidence detected in terms of cerebellar asymmetry between sagittal and axial plane estimates in the cases with vertigo. There was statistical significance between the right and left cerebellum in both the patient and control groups ( $p=0.023$ ), however, the difference did not change according to gender. There were no statistically significant age and gender dependent cerebellar atrophy and asymmetry between BPPV and control subjects.

**Conclusions:** There was no cerebellar atrophy and asymmetry between BPPV and age matched control groups. The stereological evaluation of hemi cerebellar symmetry and atrophy in humans is important for both clinicians and anatomists. The technique is simple, inexpensive, and reliable.

*Neurosciences 2011; Vol. 16 (4): 358-362*

*From the Departments of Anatomy (Gocmen-Mas), Otolaryngology (Kabveci, Altuntas), Neurosurgery (Karabekir), and Neurology (Kusbeci), School of Medicine, Kocatepe University, Afyonkarahisar, and the Department of Biostatistics (Yazici), School of Medicine, Baskent University, Ankara, Turkey.*

*Received 3rd April 2011. Accepted 12th September 2011.*

*Address correspondence and reprint request to: Asst. Prof. Nuket Gocmen-Mas, Department of Anatomy, School of Medicine, Kocatepe University, Afyonkarahisar, Turkey. Tel. +90 (272) 2463301 Ext. 1043. Fax. +90 (272) 2463300. E-mail: nuketmas@gmail.com*

**Disclosure.** The authors have no conflicting interests, and are not supported or funded by any company.

Nearly 20-30% of patients suffer from dizziness and vertigo in the general population.<sup>1</sup> As a subtype of dizziness, vertigo, determined as an illusory sensation of motion, may occur in peripheral and central vestibular pathologies. Acute vestibulopathy occurs as an acute or subacute onset of vertigo, dizziness, or imbalance with or without postural or autonomic signs, ocular motor, or sensorial symptoms. Pathological changes of various peripheral or central vestibular structures such as labyrinth, vestibular nerve, vestibular nuclei, cerebellum or ascending pathways to the thalamus and the cortex may cause acute vestibular lesions. Benign paroxysmal positioning vertigo (BPPV), Ménière's disease, perilymph fistula, vestibular neuritis, superior canal dehiscence syndrome, and vestibular paroxysmia are generally named acute peripheral disorders.<sup>2,3</sup> Acute vestibular lesions, such as peripheral benign paroxysmal positional vertigo, may result from a hypofunction or from pathological excitation of the cerebellum.<sup>3</sup> Detailed volumetric knowledge of the cerebellum, and changes in morphology related to gender in adult patients is critical to a reliable diagnosis and surgical intervention. Asymmetrical changes in the cerebellar morphology may result from some pathological diseases such as epilepsy, cerebellar hypoplasia, schizophrenia, hemimegalencephaly, autism, dyslexia, drug abuse, alcoholism, bipolar disorder, brain injuries, or tumors.<sup>1</sup> The volume of brain structures can be estimated by combining the sectional radiological imaging methods with the Cavalieri principle of stereological volume estimation, as described in previous studies.<sup>4-7</sup> However, there is limited data in the literature on the evaluation or influence of cerebellar volumetry in BPPV disease using the stereological technique. We aimed to evaluate the gender dependent cerebellar, and hemi cerebellar volumes of BPPV cases using a stereological method on MRI.

**Methods. Clinical data.** We evaluated the archive records of 15 right handed (7 males, 8 females) adult patients with peripheral BPPV aged between 18-71 years admitted to the Departments of Otolaryngology, Neurology, and Neurosurgery in Afyon Kocatepe University Faculty of Medicine, Afyonkarahisar, Turkey with complaints of vertigo between January 2004 and December 2008. The patients were matched with 14 right handed (7 males, 7 females) healthy controls aged 18-52 years. The Kocatepe University ethics committee approved the study. All the patients underwent oto-neurological examination, and MRI. We excluded patients with a history of infections, trauma, medications, cerebrovascular disease, multiple sclerosis, epilepsy, cerebellar or cerebellopontine angle tumors, spondylosis, depressive state, poor vision, orthostatic

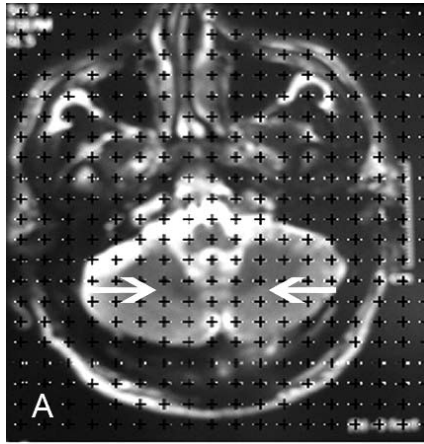
hypotension, whiplash injury, acute vestibular disorders such as neuritis, peripheral cochleovestibular syndromes, vestibular migraine, or low cerebrospinal fluid syndrome for both the control and study groups. Patients who had a lifetime history that included neurological illness, head injury, substance abuse, epilepsy, schizophrenia or bipolar disorder were excluded from the study. Patients were also questioned regarding headache, photophobia, phonophobia, syncope, or any other neurological signs to exclude central and migrainous causes of vertigo. Fifteen right-handed patients with probable BPPV were included in the study. Fourteen right-handed healthy subjects were evaluated as the control group. We retrospectively choose patients from the archive whose diagnosis was confirmed by the Dix-Hallpike test. The study group included patients whose differential diagnosis was also checked from the archive for history, physical, otolaryngological, and neurological examination, and confirmed by relevant investigations including laboratory, and audiovestibular tests. Recorded laboratory tests showed no signs of any metabolic disease or anemia. Normal otoscopy findings, briefness of the duration of vertigo, and characteristic nystagmus accompanied the BBPV diagnosis.

**Magnetic resonance image data.** We retrospectively examined the MR images of all the subjects. According to the opinion of a radiology specialist, standard T1-weighted axial and sagittal plane (5 mm) slices were obtained to compute cerebellar hemisphere volumes. All studies were performed with a 1.5-T MR machine (Philips Systems, Heerlen, The Netherlands).

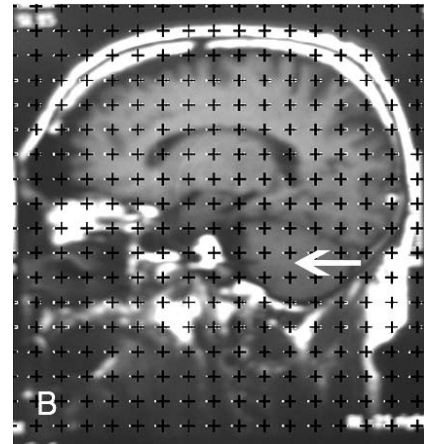
**Stereological analysis.** Both whole, and hemi cerebellar volumes computed from each image were measured 3 times by 3 observers using a stereological method. All measurements were performed blinded to subject details and the results of other measurements. An optimal plan was taken as the smallest diameter of anisotropic structures that can be measured in volumetric analysis of sagittal and axial cranial MRI sections. Original MR images were exported as tif image files and further stereological analysis was carried out on MRI scans. A uniform point-grid with a point associated area of 0.625 cm<sup>2</sup> was randomly superimposed on each MR image using the "Grid" plug-in installed. Points hitting the cerebella were manually counted for volume estimation, as previously described by Karabekir et al.<sup>1</sup> A mean axial and sagittal volumetric value was obtained from for each case. Volume estimation was accomplished by Cavalier's principle as described previously,<sup>1,6-8</sup> using the formula given below:

$$V = t \times [((SU) \times d) / SL] \times \Sigma P$$

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 2 points in the point grid, "SL"



**Figure 1** - Right and left hemi cerebellum have been shown using the stereological point counting method on the T1 weighted axial image.



**Figure 2** - The cerebellum has been indicated by arrow using the stereological point counting method on the T1 weighted sagittal image.

is the scale length (the actual measure of the scale on MRIs), and “P” is the number of points counted. To evaluate the hemispheric asymmetry between cerebellar hemispheres, the middle sections were identified by clear visualization of the cerebral aqueduct.<sup>1</sup> Figures 1 & 2 demonstrate the stereological point counting method of the cerebellum.

**Statistical analysis.** Distributions of the variables were analyzed using the Shapiro-Wilks normality test. Homogeneity of the groups’ variances was controlled by Levene’s test. Gender and age of groups were also compared by the Mann-Whitney U test. Parametric test assumptions were satisfied for other variables, and differences between left and right cerebellum volume mean of the control and vertigo groups according to gender were analyzed by 3 factorial repeated measures analysis of variance. Results were expressed as number of observations (n) and mean ± standard deviation (SD), and 95% confidence interval. P-value less than 0.05 was considered statistically significant. All statistical analyses were performed with the Statistical Package for the Social Sciences, version 17.0 (SPSS Inc, Chicago, IL, USA).

**Results.** According to the records, only 2 of the patients’ audiologic tests had high frequency sensorineural hearing loss resulting from former acoustic trauma. All the cases showed torsional horizontal nystagmus according to the Dix-Hallpike test, a characteristic sign of BPPV. Nine patients had an affected left ear, and 6 patients had an affected right ear. The mean age of the patients was 42±16.47 (±SD), and 39.07±14.29 (±SD) for the controls, with no statistically significant difference. There was statistical significance between right and left cerebellum volumes in both patient and

control groups ( $p=0.023$ ), however, it did not change according to gender. There was no statistical significance between the right and left hemisphere ratios in male and female vertigo, or control subjects. Although the right hemi cerebellum volumes of the subjects with BPPV and controls were smaller than the left hemi cerebellum volumes, there was no statistically significant quantitative evidence detected in terms of cerebellar asymmetry between sagittal and axial plane estimates in the cases with vertigo. There were also no statistically significant differences by gender in both the cases with BPPV and control subjects. Table 1 presents the mean values of axial and sagittal slices according to gender.

**Discussion.** Age or gender related volumetric differences in brain anatomy or volumetric brain analyses in many disorders are of interest. Delineating the anatomical cerebellar volume occurring in neuropsychiatric diseases is of significance for both the anatomists and clinicians. The MRI analysis allows determining of quantitative measurement changes

**Table 1** - Mean volume values (cm<sup>3</sup>) of the control and BPPV groups’ cerebellum hemispheres according to gender.

| Gender | Control<br>mean±SD (95% CI) |                             | BPPV subjects<br>mean±SD (95% CI) |                             |
|--------|-----------------------------|-----------------------------|-----------------------------------|-----------------------------|
|        | Left hemi cerebellum        | Right hemi cerebellum       | Left hemi cerebellum              | Right hemi cerebellum       |
| Male   | 51.56±4.17<br>(47.70-55.41) | 46.50±4.84<br>(42.03-50.97) | 52.77±5.17<br>(47.99-57.54)       | 49.93±7.95<br>(42.09-56.78) |
| Female | 52.32±5.51<br>(47.22-57.44) | 47.05±6.39<br>(41.14-52.95) | 50.69±9.1<br>(43.09-58.28)        | 48.47±9.51<br>(40.53-56.42) |

BPPV - benign paroxysmal positional vertigo, SD - standard deviation, CI - confidence interval

of the cerebella, and morphological evaluation of the brain and its substructures *in vivo*.<sup>6</sup> Studies report the stereological quantitative evaluation of the brain as the site of morphological changes in central causes of vertigo,<sup>1</sup> or other neurodegenerative disease.<sup>4,5,9-11</sup> Paroxysmal peripheral positional vertigo is the most commonly observed form of labyrinthine vertigo and is definitely the balance disorder affecting cerebellar volume. Although in most cases BPPV is considered to be idiopathic, various etiological factors such as trauma, viral, dysendocrine, dysmetabolic, deficiency-related autoimmune factors, post-surgery, vertebrobasilar insufficiency, viral labyrinthitis, vestibular degeneration, and prolonged bed-rest may play a role in defining the disorder.<sup>12</sup> Imaging is not useful in the routine diagnosis of BPPV because there are no radiological findings diagnostic for BPPV. Radiographic imaging of the CNS should be carried out when there is a clinical history compatible with BPPV, and in those who also demonstrate additional neurological symptoms atypical for BPPV. The vertigo may be in conjunction with, or as sequelae to, other vestibular disorders. In small case series, positional vertigo and nystagmus were associated with neurovascular compression of cranial nerve 8, vestibular schwannoma, Arnold Chiari malformation, and a variety of cerebellar disorders.<sup>2,13</sup>

Quantitative analysis of MR imaging can improve its diagnostic yield and has the potential to further elucidate the etiology of disease. There are several previous studies describing different morphometric techniques in the brain.<sup>6,14,15</sup> However, there is ambiguity and diversity on the definitions of volumetric analysis methods of brain structures in the literature, which are frequently referred to as “traced”, “automatic” (atlas-based), “planimetry”, “three-dimensional” and so forth. Some authors claim that the automatic method is rapid, efficient, and unbiased, and not subject to the problems of rater drift, or constrained by potentially poor interpreter reliability. However, others noted the traced measurements as a “gold standard” against the automatic method.<sup>16</sup> These methods each segmented one target object on each MR image obtained by different sequences. Recently, authors reported the development of morphology-based brain segmentation for data on CT images using a fully automatic technique. The brain segmentation and calculation of the volume of the structures was carried out with the help of specialized software.<sup>17</sup> Although age or gender related volumetric differences in the cerebella anatomy of individuals has been investigated by many researchers,<sup>1,6-8,10</sup> there is a lack of data on asymmetrical volume evaluation in cases with BPPV via a stereological technique. Thus, differing from previous studies, we adopted the stereological measurement technique that was firstly used in evaluation of cerebellar

asymmetry by Gocmen-Mas.<sup>6</sup> Cavalieri’s principle of the stereological approach by point counting consists of overlying each selected section with a regular grid of test points, which is randomly positioned. The Cavalieri theorem of systematic sampling in combination with point counting is a reliable, simple, inexpensive, and efficient method for estimating volumes in MRI. This approach also takes less time.<sup>18,19</sup> The requirement for the application of the stereological method is an entire set of 2-dimensional slices through the object, provided they are parallel, separated by a known distance, and begin randomly within the object, criteria that are met by the standard MR imaging technique.<sup>20,21</sup>

The cerebellum was selected as a region of interest because it plays an important role in both the coordination of motor actions and the processing of cognitive information via indirect projections to cortical motor areas and prefrontal cortex. Neuroanatomical, neuroimaging, and behavioral reports of the cerebella in cognitive and language functions increasingly identify the cerebellum as the site of morphological changes occurring in neuropsychiatric diseases.<sup>6</sup> The cerebellum does not have a symmetrical morphology even in healthy subjects according to many authors. As an example, dextrals show more asymmetry than non-dextrals.<sup>1,6</sup> A detailed knowledge of the asymmetrical structure of the cerebellum and changes in its morphology related to gender parameters are of diagnostic importance. Various authors reported that cerebral lesions may cause positional vertigo, known as central paroxysmal positional vertigo.<sup>22-24</sup> Shoman and Longridge<sup>25</sup> drew attention to the diagnosis of cerebellar vermis lesions and tumors of the fourth ventricle by presenting 2 cases of patients with positional nystagmus of the so called benign paroxysmal type.<sup>25</sup> Latency, course, and duration of nystagmus do not permit differentiation between BPPV and central paroxysmal positioning nystagmus.<sup>3</sup> Therefore, we aimed to evaluate whether or not the cerebellum showed asymmetrical morphology in benign peripheral vertigo cases. Karabekir et al<sup>1</sup> found no significant quantitative evidence in terms of cerebella asymmetry between sagittal plane estimates in cases with central causes of vertigo in both genders. They also found that there were no statistically significant differences according to gender between both vertigo and control subjects. According to our data, there were no asymmetrical changes with regard to BPPV in the cerebellum. Some authors claim that female subjects have significantly smaller cerebellar volumes compared with males of similar age in healthy cases.<sup>6</sup> Although the present study has some methodological similarities with many previous studies,<sup>1,4-11,19</sup> we did not found any significant gender differences in the cases with BPPV.

Obviously, like all studies, our study also has some limitations, one of the most important of which is the sample size of our study and control groups. Further retrospective or/and prospective clinical meta-analytic studies involving a greater number of patients, BPPV subjects, and other vertigo subtypes will help to extend and support our findings.

In conclusion, the stereological method helps clinicians and anatomists define changes in hemi cerebellar volumes for evaluating volumetric differences or variations and asymmetric pathologies, such as tumors, hematomas, neurodegenerative disorders, and so forth. The method is simple, cheap, safe, and rapid.

**Acknowledgments.** *Many thanks are expressed to Dr. Aylın Yucel, Consultant Radiologist, for his skillful radiological assistance.*

## References

- Karabekir HS, Mas NG, Yilmaz OK, Bař O, Ertekin T, Yazici AC, et al. Evaluation of cerebellar asymmetry with vertigo cases: a stereological study. *Turk Neurosurg* 2009; 19: 15-20.
- Bhattacharyya N, Baugh RF, Orvidas L, Barrs D, Bronston LJ, Cass S, et al. Clinical practice guideline: benign paroxysmal positional vertigo. *Otolaryngol Head Neck Surg* 2008; 139: 47-81. Review.
- Strupp M, Arbusow V. Acute vestibulopathy. *Curr Opin Neurol* 2001; 14: 11-20.
- Yilmaz-Kusbeci O, Gocmen-Mas N, Yucel A, Karabekir HS, Ertekin T, Yazici AC. Evaluation of cerebellar and cerebral volume in migraine with aura: a stereological study. *Cerebellum* 2010; 9: 345-351.
- Kusbeci OY, Bas O, Gocmen-Mas N, Karabekir HS, Yucel A, Ertekin T, et al. Evaluation of cerebellar asymmetry in Alzheimer's disease: a stereological study. *Dement Geriatr Cogn Disord* 2009; 28: 1-5.
- Gocmen-Mas N, Pelin C, Canan S, Yazici AC, Zagyapan R, Senan S, et al. Stereological evaluation of volumetric asymmetry in healthy human cerebellum. *Surg Radiol Anat* 2009; 31: 177-181.
- Acer N, Sahin B, Usanmaz M, Tatođlu H, Irmak Z. Comparison of point counting and planimetry methods for the assessment of cerebellar volume in human using magnetic resonance imaging: a stereological study. *Surg Radiol Anat* 2008; 30: 335-339.
- Ekinci N, Acer N, Akkaya A, Sankur S, Kabadayi T, Sahin B. Volumetric evaluation of the relations among the cerebrum, cerebellum and brain stem in young subjects: a combination of stereology and magnetic resonance imaging. *Surg Radiol Anat* 2008; 30: 489-494.
- Bas O, Acer N, Mas N, Karabekir HS, Kusbeci OY, Sahin B. Stereological evaluation of the volume and volume fraction of intracranial structures in magnetic resonance images of patients with Alzheimer's disease. *Ann Anat* 2009; 191: 186-195.
- Andersen BB, Gundersen HJ, Pakkenberg B. Aging of the human cerebellum: a stereological study. *J Comp Neurol* 2003; 466: 356-365.
- Andersen BB, Pakkenberg B. Stereological quantitation in cerebella from people with schizophrenia. *Br J Psychiatry* 2003; 182: 354-361.
- Faralli M, Ricci G, Molini E, Bressi T, Simoncelli C, Frenguelli A. Paroxysmal positional vertigo: the role of age as a prognostic factor. *Acta Otorhinolaryngol Ital* 2006; 26: 25-31.
- Gacek RR. Pathology of benign paroxysmal positional vertigo revisited. *Ann Otol Rhinol Laryngol* 2003; 112: 574-582.
- Zhao L, Ruotsalainen U, Hirvonen J, Hietala J, Tohka J. Automatic cerebral and cerebellar hemisphere segmentation in 3D MRI: adaptive disconnection algorithm. *Med Image Anal* 2010; 14: 360-372.
- Akhondi-Asl A, Jafari-Khouzani K, Elisevich K, Soltanian-Zadeh H. Hippocampal volumetry for lateralization of temporal lobe epilepsy: automated versus manual methods. *Neuroimage* 2011; 54 Suppl 1: S218-S226.
- Mas N, Senan S, Firat M, Tuncel M, Basar R. Evaluation of human brain volume by the tracing technique. *Neurosciences (Riyadh)* 2009; 14: 96-97.
- Jiang SF, Chen WF, Feng QJ, Yang SH. [Automatic extraction and segmentation of the intracranial structure from cerebral computed tomography]. *Nan Fang Yi Ke Da Xue Xue Bao* 2007; 27: 1805-1808.
- Odaci E, Sahin B, Sonmez OF, Kaplan S, Bas O, Bilgic S, et al. Rapid estimation of the vertebral body volume: a combination of the Cavalieri principle and computed tomography images. *Eur J Radiol* 2003; 48: 316-326.
- Sahin B, Acer N, Sonmez OF. Comparison of four methods for the estimation of intracranial volume: a gold standard study. *Clin Anat* 2007; 20: 766-773.
- Sahin B, Ergur H. Assessment of the optimum section thickness for the estimation of liver volume using magnetic resonance images: a stereological gold standard study. *Eur J Radiol* 2006; 57: 96-101.
- Roberts N, Puddephat MJ, McNulty V. The benefit of stereology for quantitative radiology. *Br J Radiol* 2000; 73: 679-697.
- Johkura K. Vertigo and dizziness associated with cerebrovascular diseases. Nihon Ishikai Zasshi. *The Journal of the Japan Medical Association* 2005; 134: 1485-1490.
- Johkura K. Central paroxysmal positional vertigo: isolated dizziness caused by small cerebellar hemorrhage. *Stroke* 2007; 38: 26-27.
- Arai M, Terakawa I. Central paroxysmal positional vertigo. *Neurology* 2005; 64: 1284.
- Shoman N, Longridge N. Cerebellar vermis lesions and tumours of the fourth ventricle in patients with positional and positioning vertigo and nystagmus. *J Laryngol Otol* 2007; 121: 166-169.