VIA MEDICA

ORIGINAL ARTICLE

Folia Morphol.
Vol. 71, No. 2, pp. 65–70

ISSN 0015–5659
www.fm.viamedica.pl

Determination of cerebellar volume in children and adolescents with magnetic resonance images

M.I. Kosar[1], K. Karacan[1], I. Otag[2], M. Isleyen[3], S. Gültürk[4], M. Cimen[1]

[1]*Department of Anatomy, Cumhuriyet University School of Medicine, Sivas, Turkey*
[2]*Vocational School of Health Services, Cumhuriyet University, Sivas, Turkey*
[3]*Department of Radiology, Elbistan State Hospital, Kahramanmaras, Turkey*
[4]*Department of Physiology, Cumhuriyet University School of Medicine, Sivas, Turkey*

[Received 6 January 2012; Accepted 12 March 2012]

Recent studies show that the cerebellum contributes to higher cognitive functions as well as its role on motor system. It is thought that higher cognitive functions continue to develop during childhood and adolescence; therefore, cerebellum develops significantly during these periods. For that reason, this study was carried out in order to determine cerebellar volumes of 90 healthy individuals (40 males, 50 females) aged between 6 and 17 years according to their gender. The individuals were divided into three age groups of 6–9, 10––13, and 14–17 years, and their cerebellar volumes were found by means of stereological methods using their magnetic resonance images. The cerebellar volumes found were compared among the groups without discriminating genders, among groups according to gender, and again according to gender within each age group. The general average cerebellar volume of the age group 10–13 years was significantly higher than the other two age groups ($p < 0.05$). When the groups were compared according to gender, there was no important difference between the groups in women ($p > 0.05$); as for men, cerebellar volume only in the age group 10–13 years was significantly higher than that in age group 6–9 ($p < 0.05$). When cerebellar volume for ages 6–17 years was compared according to gender (without dividing into age group) there was no significant difference between men and women ($p > 0.05$). It was seen that the cerebellum develops from childhood to adolescence, and reaches peak levels between the ages 10–13 years for both genders. (Folia Morphol 2012; 71, 2: 65–70)

Key words: cerebellum, cerebellar volume, stereology, magnetic resonance imaging

INTRODUCTION

In recent years, the traditional motor role of the cerebellum has been expanded to include cognitive and emotional functions [9, 12, 23]. The majority of these functions experience dramatic changes during childhood and adolescence [31]. Data gained from a clinic population served as the basis for research examining cognitive and motor functions. Children with attention deficit hyperactivity disorder and autism spectrum disorders show deficiency in motor functions together with cognitive and affective disorder [21].

Address for correspondence: M.I. Kosar, MD, Assist. Prof., Department of Anatomy, Cumhuriyet University School of Medicine, TR-58140 Sivas, Turkey, tel: +90 346 219 10 10/1062, e-mail: ilkaykosar@gmail.com

Developmental changes seen in cerebellar volume (CV) may serve as the basis for cognitive functions in childhood [21]. The human brain works with a relationship between cognitive functions and motor functions and as a system including the neocortex, subcortex, and cerebellum [11, 21]. In the brain, the prefrontal cortex plays a basic role in cognitive control [19, 30]. In many studies, cross connections were found between the cerebellum and prefrontal cortex and posterior parietal cortex. The studies carried out using virus markers in monkeys found that there is a connection between the monkey prefrontal region and the cerebellum [18]. The cerebellum can receive information through cortico-ponto-cerebellar ways and affect the cognitive region of the brain through cerebello-thalamo-cortical ways [3]. The connection of the cerebellum with the prefrontal cortex may show its role in cognitive function. Afferent information may go to the lateral cerebellar cortex from peripheral and central nervous systems; however, outgoing information goes to the dentate nucleus, and then the majority of this information goes to the neocortex by means of the thalamus [15].

The clinical table developing due to acquired cerebellar lesions in children and adults and symptoms such as impairments in executive, visual-spatial, and linguistic abilities, with affective disturbance ranging from emotional blunting and depression, was defined by Schmahmann and Sherman [27] under the name of cerebellar cognitive affective syndrome (CCAS).

Higher cognitive function continues to develop during childhood and adolescence, and it is thought that the cerebellum develops significantly during these periods. In the study performed by Pangelinan et al. [21] in children aged between 6–13, a significant positive relationship was found between age and the volume of total and frontal white matter, parietal white matter, and the cerebellum, while a significant negative relationship was found for parietal grey matter and age. Again, in the same study, a significant relationship was found between general cognitive ability (IQ) and the volume of subcortical brain structures (cerebellum and caudate).

Prefrontal-thalamic-cerebellar structures are the regions that mature actively during adolescence [5]. In our study, we aimed to determine the volume of the cerebellum by stereological means according to gender and the three determined age groups in order to assess the development of the cerebellum during childhood and adolescence.

MATERIAL AND METHODS

Magnetic resonance imaging (MRI) of 90 healthy children (40 males, 50 females) aged between 6 and 17 years were examined in our study. All subjects were admitted to the Department of Radiology in Cumhuriyet University, Faculty of Medicine between March 2007 and April 2008. The local Human Ethics Committee approved the study. Only subjects who met all of the following conditions were used in this study: 1) subjects had no previous brain disease; 2) no signal abnormality and cerebral tumours, infarction or haemorrhage were found on MRI; 3) no history of prenatal confounds that could influence brain maturation, such as prenatal exposure to substances or pregnancy and birth complications; 4) no positive trauma or maltreatment history; 5) no significant medical, neurological, or psychiatric disorder or history of head injury or loss of consciousness. MRIs were divided into the previously determined age groups (6–9 years, 10–13 years, and 14–17 years) taking into consideration the gender difference.

Images were acquired with a 1.5-T commercial MRI machine (Exelart, Toshiba, Tokyo, Japonya) with a quadrature head coil. The imaging protocol included axial T2 weighted images. The scanning was performed with the following parameters: spin-echo axial, repetition time (TR) = 5000 ms; echo time (TE) = 94 ms; Flip angle (FA) = 90/160; NEX = 2; field of view (FOV) = 180 × 220 mm; matrix = 224 × 320 and 5-mm section thickness, 1.2-mm intersection gap.

Stereological volume measurements were based on the Cavalier principle. The technique is simple and reliable [8]. According to the rule of this principle, sections were taken equidistant, parallel, and serial to most accurately calculate the volume of interest [17, 20]. All CVs were estimated from each image using the point counting technique. A square grid test system with d = 0.3 cm between test points was used to estimate the sectioned surface area of the slice. The films were placed on a negatoscope and the transparent square grid test system with d = 0.3 cm between test points was superimposed, randomly covering the entire image frame. In measuring, points matching each cerebellum grid were counted three times and the number of points matching each cerebellum point was estimated by taking the average of this count. Following the point numbers, the frame area was calculated. To estimate cerebellar volume, the modified formula used for volume estimation of radiological images was applied [10, 26]:

$$V = t \times [((SU) \times d)/SL]^2 \times \Sigma P$$

Table 1. Mean cerebellar volume according to age groups [cm^3]

Age groups	Sex	n	Mean	SD
6–9	Female	11	120.08	8.99
	Male	19	119.05	15.66
	Total	30	119.43	13.42
10–13	Female	21	127.53	11.74
	Male	9	133.87	10.82
	Total	30	129.44	11.66
14–17	Female	18	120.78	13.05
	Male	12	122.47	10.75
	Total	30	121.45	12.01
6–17	Female	50	123.46	12.00
	Male	40	123.41	14.30
	Total	90	123.44	13.00

where 't' is the section thickness (including interval) of consecutive sections, 'SU' the scale unit of the printed film, 'd' the distance between the test points of the grid, 'SL' the measured length of the scale printed on the film, and 'ΣP' the total number of points hitting the sectioned cut surface areas of cerebellum. All data for calculation of CV were entered in the appropriate place on a macro program that was prepared using Excel and the final data were obtained automatically.

The results were evaluated by SPSS software v. 16. CV values were expressed as mean ± SD. Two-way ANOVA with *post hoc* Tukey test were used to analyse the CVs of the groups. CV values of female and male subjects in all age groups were analysed with Mann-Whitney U test. A p-value < 0.05 was considered to be statistically significant.

RESULTS

The average CV values found according to gender in all of the three age groups are shown in Table 1. When the CV values of the three age groups are compared without discriminating gender, there is statistical difference between age groups 6–9 and 10–13 years and again between age groups 10–13 and 14–17 years ($p < 0.05$). On the other hand, there is no statistical difference between age groups 6–9 and 14–17 years ($p > 0.05$). Accordingly, average CV of the age group 10–13 years was significantly higher than the other two groups (Fig. 1).

When each age group is compared according to gender within itself, there is no statistical difference between men and women in all of the three age groups ($p > 0.05$). When the CVs of women are compared among the groups, there is no statistical difference ($p > 0.05$). When CVs of men are compared among the groups, there is a statistical difference between age groups 6–9 and 10–13 years while there is no difference between the other groups. The CV of men in the age group 10–13 years was significantly higher than those in the age group 6–9 years ($p < 0.05$) (Fig. 1). When the CV of the age group 6–17 years is compared according to gender (without dividing into age group), no statistically significant difference was found between men and women ($p > 0.05$).

DISCUSSION

During ordinary childhood, brain development is a complex and a dynamic process [24]. From birth

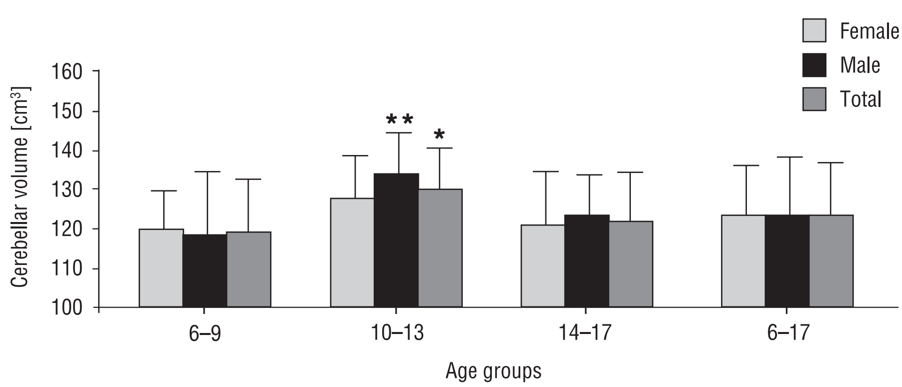

Figure 1. Mean cerebellar volume according to age groups [cm^3]; *mean total cerebellar volume of the age group 10–13 years is significantly higher than the other two groups ($p < 0.05$); **there is a significant difference between age group 6–9 and 10–13 years in males ($p < 0.05$).

until teenage years, brain volume increases four times and a significant increase in motor and cognitive abilities also occurs. This increase in volume is not uniform but different in cortical and subcortical regions [13]. Adolescence is the transit period from childhood to adulthood during which there is a significant development at the behavioural and cognitive level relating to the changes in brain structures [14, 28].

Human neuroimaging studies show that in higher cognitive functions, not only prefrontal regions but also striato-thalamo-cortical and cerebello-thalamo-cortical stages give service [14]. As supported clinically, Riva et al. [25] stated in their study that cognitive and behavioural disorders developed following cerebellar lesions, and that the symptoms occurring according to topography of lesions were different. Similarly, a study by Aarsen et al. [1] found that children treated for cerebellar tumours with surgery exhibited cognitive impairments.

There is a relationship between lower CV and deficiencies in neuropsychological performance [2]. It was shown that CCAS observed after acquired cerebellar lesions develop in children and adults. Moreover, it was stated that the symptoms shown by those with cerebellar malformation were more serious but less specific [29]. MRI studies have demonstrated smaller total cerebellar and vermal volumes in schizophrenia, mood disorders, and attention deficit hyperactivity disorder [3].

Spurts in the number of glial cells in the brain and brain stem start earlier than the cerebellum. Spurts in the cerebellum start later but complete earlier. It is estimated that at around 18 months, while the cerebellum cell content is at adult level, it reaches approximately 60% of adult level in the proensephalon and brain stem [16]. While normal cerebral cortical development shows a linear increase in white matter, it is characterised by an increase in the preadolescent period and a decrease in the post-adolescent period in grey matter. This change in grey matter may be a reflection of firstly synaptic arborisation and then pruning, and a linear increase in white matter may be a sign of myelination events increasing during adolescence [7].

Although the cerebellum is one of the brain structures that becomes different first, it is also one of the structures which matures last, like the prefrontal cortex [6, 33].

Tiemeier et al. [31] found in their study that total CV follows a developmental orbit like an inverse letter U and reaches peak levels at the age of 11.8 years in females and 15.6 years in males, and furthermore, CV is 10% to 13% higher in males due to age. They also stated that CV, as a whole, has a longer development process as it reaches peak volume after the brain. In our study, it was seen that CVs reached peak levels in the age group 10–13 years for both genders, and the values in this age group were significantly higher than in the other two age groups.

Vannucci et al. [32] found in their study that CV increased by 300% between birth and 12-months, 50% between the following 12 and 18 months, and there was a very distinctive graded increase during childhood and the early adolescence period.

Wu et al. [34], in their study performed with 50 children aged between 0.2–12.7 years, observed that the most significant increase in CV was during the first two years, and found in the same study that cerebellar development in females was behind that of males; however, it reached the volume of males at around 12 years. Caviness et al. [4] in a cross-sectional sample of 30 normal children (15 males, 15 males) aged 7–11 years found that the cerebellum was at adult volume in females but not males at this age range.

Gender differences in the cerebellum are lower than in the brain [31]. In spite of the studies showing that the CV is higher in males, in our study, no significant difference was detected between females and males in all of the three age groups although the volume was higher in males in the age groups 10–13 and 14–17 years. Giedd et al. [7] used MRIs obtained from 104 healthy children and adolescents aged 4–18 years and found that CV in males was larger than in females.

Some studies were carried out researching the effect of birth time on cerebellum development during adolescence. Parker et al. [22] CVs volumes between those who were very preterm (VPT) and those who were term-born, and measured CVs of both groups twice in adolescents and adults. In this study, grey and white matter volumes showed similar development patterns in both of the groups. However, grey and white matter volumes were significantly smaller in the VPT group in adolescence and young adulthood. The average CV was not significant between the two groups in both of the measurements, and it was shown by the results obtained that CV was constant in term-born adolescents. Similarly, Alin et al. [2] determined in their study that CV of terms was significantly higher than in preterms during adolescence.

In ordinary brain development, childhood and adolescence are important periods. Adolescence is the period during which important neurobiological and behavioural changes occur. Brain imaging studies have shown that the human brain, especially the prefrontal cortex and cerebellum continue to develop during adolescence years. Although the cerebellum accounts for only 10% of the total brain volume, a matured cerebellum contains more than half of all neurons [23]. Therefore, it can be estimated that it plays more roles than the known motor functions. Nonetheless, recent studies have shown its role on cognitive functions and affection in addition to motor function. This study has shown that there is an increase in CV in healthy individuals between ages of 6–14 years in both genders, and that it reaches peak levels between 10–13 years.

REFERENCES

1. Aarsen FK, Van Dongen HR, Paquier PF, Van Mourik M, Catsman-Berrevoets CE (2004) Long-term sequelae in children after cerebellar astrocytoma surgery. Neurology, 62: 1311–1316.
2. Allin M, Matsumoto H, Santhouse AM, Nosarti C, AlAsady MH, Stewart AL, Rifkin L, Murray RM (2001) Cognitive and motor function and the size of the cerebellum in adolescents born very pre-term. Brain, 124 (Part 1): 60–66.
3. Baldaçara L, Borgio JG, Lacerda AL, Jackowski AP (2008) Cerebellum and psychiatric disorders. Rev Bras Psiquiatr, 30: 281–289.
4. Caviness VS Jr, Kennedy DN, Richelme C, Rademacher J, Filipek PA (1996) The human brain age 7–11 years: a volumetric analysis based on magnetic resonance images. Cereb Cortex, 6: 726–736.
5. De Bellis MD, Narasimhan A, Thatcher DL, Keshavan MS, Soloff P, Clark DB (2005) Prefrontal cortex, thalamus, and cerebellar volumes in adolescents and young adults with adolescent-onset alcohol use disorders and comorbid mental disorders. Alcohol Clin Exp Res, 29: 1590–1600.
6. Diamond A (2000) Close interrelation of motor development and cognitive development and of the cerebellum and prefrontal cortex. Child Dev, 71: 44–56.
7. Giedd JN, Snell JW, Lange N, Rajapakse JC, Casey BJ, Kozuch PL, Vaituzis AC, Vauss YC, Hamburger SD, Kaysen D, Rapoport JL (1996) Quantitative magnetic resonance imaging of human brain development: ages 4–18. Cereb Cortex, 6: 551–560.
8. Gocmen-Mas N, Kusbeci OY, Karabekir HS, Ertekin T, Yucel A, Yazici AC (2011) Volumetric evaluation of hemicerebellar changes in migraine patients without aura. Folia Morphol, 70: 235–239.
9. Gottwald B, Wilde B, Mihajlovic Z, Mehdorn HM (2004) Evidence for distinct cognitive deficits after focal cerebellar lesions. J Neurol Neurosurg Psychiatry, 75: 1524–1531.
10. Gundersen HJG, Jensen EBV, Kýeu K, Nielsen J (1999) The efficiency of systematic sampling in stereology-reconsidered. J Microscopy, 193: 199–211.
11. Hatta T, Masui T, Ito Y, Ito E, Hasegawa Y, Matsuyama Y (2004) Relation between the prefrontal cortex and cerebro-cerebellar functions: evidence from the results of stabilometrical indexes. Appl Neuropsychol, 11: 153–160.
12. Hopyan T, Laughlin S, Dennis M (2010) Emotions and their cognitive control in children with cerebellar tumors. J Int Neuropsychol Soc, 16: 1027–1038.
13. Johnson MH (2001) Functional brain development in humans. Nat Rev Neurosci, 2: 475–483.
14. Luna B, Sweeney JA (2001) Studies of brain and cognitive maturation through childhood and adolescence: a strategy for testing neurodevelopmental hypotheses. Schizophr Bull, 27: 443–455.
15. MacLeod CE, Zilles K, Schleicher A, Rilling JK, Gibson KR (2003) Expansion of the neocerebellum in Hominoidea. J Hum Evol, 44: 401–49.
16. Malina MR (2004) Motor development during infancy and early childhood: overview and suggested directions for research. Internat J Sport Health Science, 2: 50–66.
17. Mayhew TM, Olsen DR (1991) Magnetic resonance imaging (MRI) and model-free estimates of brain volume determined using the cavalieri principle. J Anat, 178: 133–144.
18. Middleton FA, Strick PL (2001) Cerebellar projections to the prefrontal cortex of the primate. J Neurosci, 21: 700–712.
19. Miller EK, Freedman DJ, Wallis JD (2002) The prefrontal cortex: categories, concepts and cognition. Philos Trans R Soc Lond B Biol Sci, 357: 1123–1136.
20. Odaci E, Bahadir A, Yildirim Þ, Sahin B, Canan S, Bas O, Bilgic S, Kaplan S (2005) Cavalieri prensibi kullanýlarak bilgisayarlý tomografi ve manyetik rezonans görüntüleri üzerinden hacim hesaplamasý ve klinik kullanýmý. Türkiye Klinikleri J Med Sci, 25: 421–428.
21. Pangelinan MM, Zhang G, VanMeter JW, Clark JE, Hatfield BD, Haufler AJ (2011) Beyond age and gender: relationships between cortical and subcortical brainvolume and cognitive-motor abilities in school-age children. Neuroimage, 54: 3093–3100.
22. Parker J, Mitchell A, Kalpakidou A, Walshe M, Jung HY, Nosarti C, Santosh P, Rifkin L, Wyatt J, Murray RM, Allin M (2008) Cerebellar growth and behavioural and neuropsychological outcome in preterm adolescents. Brain, 131 (Part 5): 1344–1351.
23. Rapoport M, van Reekum R, Mayberg H (2000) The role of the cerebellum in cognition and behavior: a selective review. J Neuropsychiatry Clin Neurosci, 12: 193–198.
24. Reiss AL, Abrams MT, Singer HS, Ross JL, Denckla MB (1996) Brain development, gender and IQ in children. A volumetric imaging study. Brain, 119 (Part 5): 1763––1774.
25. Riva D, Giorgi C (2000) The cerebellum contributes to higher functions during development: evidence from a series of children surgically treated for posterior fossa tumours. Brain, 123 (Part 5): 1051–1061.

26. Sahin B, Ergur H (2006) Assessment of the optimum section thickness for the estimation of liver volume using magnetic resonance images: a stereological gold standard study. Eur J Radiol, 57: 96–101.
27. Schmahmann JD, Sherman JC (1998) The cerebellar cognitive affective syndrome. Brain, 121 (Part 4): 561–579.
28. Steinlin M (2007) The cerebellum in cognitive processes: supporting studies in children. Cerebellum, 6: 237–241.
29. Tavano A, Grasso R, Gagliardi C, Triulzi F, Bresolin N, Fabbro F, Borgatti R (2007) Disorders of cognitive and affective development in cerebellar malformations. Brain, 130 (Part 10): 2646–2660.
30. Thomsen T, Specht K, Rimol LM, Hammar A, Nyttingnes J, Ersland L, Hugdahl K (2004) Brain localization of attentional control in different age groups by combining functional and structural MRI. Neuroimage, 22: 912––919.
31. Tiemeier H, Lenroot RK, Greenstein DK, Tran L, Pierson R, Giedd JN (2010) Cerebellum development during childhood and adolescence: a longitudinal morphometric MRI study. Neuroimage, 49: 63–70.
32. Vannucci RC, Barron TF, Lerro D, Antón SC, Vannucci SJ (2011) Craniometric measures during development using MRI. Neuroimage, 56: 1855–1864.
33. Wang VY, Zoghbi HY (2001) Genetic regulation of cerebellar development. Nat Rev Neurosci, 2: 484–491.
34. Wu KH, Chen CY, Shen EY (2011) The cerebellar development in chinese children-a study by voxel-based volume measurement of reconstructed 3D MRI scan. Pediatr Res, 69: 80–83.